80 Years of the Faculty of Medicine in Hradec Králové

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Last year marked 80 years since Edvard Beneš, President of the Czechoslovak Republic, signed a decree establishing the medical faculty in Hradec Králové as a branch of the Faculty of Medicine at Charles University in Prague. This was the beginning of medical education in the city and the wider East Bohemian region.

The decision to establish the faculty here was no coincidence.

For centuries, Hradec Králové was an important fortified town in the Austrian Empire, and all aspects of life in the town and its surroundings were subordinated to this fact. This situation lasted until the end of the 19th century, when the fortress was dismantled. It was only after this that the town and region underwent rapid development, a process that continued during the First Republic.

The region's development led to a sharp increase in population, creating a need for better, more accessible healthcare. Thanks to the significant support and efforts of city officials, one of the largest and most modern hospitals in what was then Czechoslovakia was built. This hospital employed a number of leading experts who, in addition to their high level of professional expertise and medical experience, were also actively involved in lecturing, publishing and social activities.

The region therefore possessed a high level of personnel, professional and material readiness to support a medical faculty. Its possible establishment was therefore discussed throughout the interwar period as part of the efforts to establish a university in Hradec Králové – or rather, a regional university in East Bohemia. However, this process was halted for six long years by a significant historical event: the occupation of the republic and its subjugation as the Protectorate as part of the German Reich.

The desperate shortage of doctors after the liberation in 1945 increased the urgency to open a medical faculty as soon as possible. The closure of universities during the occupation, violent deaths on the battlefield, in concentration and labour camps, the post-war displacement of the German population and waves of emigration all contributed to the critical shortage of physicians. Given these circumstances, it was only logical that the city of Hradec Králové was chosen to establish a medical faculty shortly after the war ended. Thanks to the extraordinary efforts of the government, the Ministry, the district and municipal authorities, representatives of higher education and leading physicians at the Hradec Králové hospital, the city became a university town 80 years ago when a branch of the Medical Faculty of Charles University was established there.

However, the beginnings were not easy. Besides having access to the state-of-the-art hospital, the school also needed adequate facilities for teaching basic theoretical subjects and high-quality teaching materials. The need for teaching facilities was resolved thanks to the opportunity to use a modern building on Šimkova Street. Built just before the war for the command corps of the Czechoslovak army, the building was seized and used by the Germans for other, more sinister purposes during the occupation. Adapting it for medical teaching was challenging, but hard work and enthusiasm resolved this issue relatively

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quickly. Leading physicians, scientists and respected experts became involved in managing individual departments and organising teaching. The level of interest in studying medicine was huge, and the teaching was of a very high standard, at the cutting edge. The faculty soon became a respected and recognised institution.

The escalation of the international political situation in the 1950s, coupled with the world's division into irreconcilable camps, led to a rapid increase in armaments, expansion of individual armies, and a simultaneous need to bolster the ranks of military doctors. In response to political demands, the Faculty of Medicine in Hradec Králové was transformed into the Military Medical Academy in 1951. Alongside a partial change in the content of teaching and research, this resulted in significant personnel changes within various departments. Unfortunately, as a result of this transformation, a number of doctors who did not wish to become professional soldiers left the faculty. However, it should be noted that despite all the political and personnel complications, the academy's professional level remained high.

Another significant milestone in the history of the Hradec Králové faculty was its return to the civilian sector in 1958, which led to the establishment of an independent Faculty of Medicine at Charles University. Basic theoretical, preclinical and clinical disciplines developed dynamically in line with the needs of modern times, and this was later supported by the opportunity to cooperate with foreign countries thanks to the partial easing of the political situation at that time. Unfortunately, the so-called 'normalisation' of the 1970s hit our entire society hard, including our faculty. Political purges led to severe staff shortages at virtually all workplaces, paralysing the development of the faculty for a long time. Recovery was slow, and the negative impact was evident for a long time.

Fundamental changes occurred following the revolutionary societal changes of 1989. Academic values were reinstated, and democratic traditions in higher education were revived. Management of the faculty and university was based on new principles, and development of individual fields, departments, institutes and clinics was no longer politically restricted. Since then, there has been noticeable and sustained positive development.

Teaching has also changed significantly thanks to modern teaching methods and programmes, sophisticated aids, computer technology and the internet. However, the most important thing that has remained unchanged since the beginnings of our faculty is the role of the teacher. Their experience, knowledge of the subject and personal approach, enabling the traditional transfer of acquired knowledge from generation to generation, remains as important as ever.

The Faculty of Medicine currently offers degree programmes in General Medicine, Dentistry, General Nursing and Midwifery. These programmes are taught in Czech and, for hundreds of foreign students, in English. The faculty also offers doctoral programmes. A total of almost 2,000 students are currently enrolled at the faculty.

However, teaching is not the only role of a modern medical faculty. Science and research are also integral to the faculty's activities as world-class research into a wide range of biomedical issues is carried out.

Adequate conditions are also necessary to support all faculty activities. This is why the faculty now offers modern facilities that are ideal for teaching medicine and conducting research. These facilities are located in a carefully renovated building on Šimkova Street and in the historic Na Hradě building, as well as in study areas at individual university hospital departments. In addition, new complexes have been gradually constructed. These include a teaching centre on the grounds of the Faculty Hospital and a joint campus for the medical and pharmaceutical faculties nearby. Completing these is now one of our most important tasks. The planned opening this year will create new opportunities for our students and staff. If all goes according to plan, the 2026/27 academic year will begin in the new premises.

Throughout its existence, the Faculty of Medicine has worked closely with the University Hospital in Hradec Králové. Cooperation between the two institutions is essential and is conducted on a consistently high professional level, with mutual respect. After all, the Faculty of Medicine cannot exist without its hospital, just as the University Hospital cannot exist without its faculty. Without a balanced and functional connection between the two, it would not be possible to fulfill their missions. And the University Hospital in Hradec Králové, which is now one of the largest and most modern hospitals in the country, is the main base for the practical training of our students.

We also successfully cooperate with other contracted hospitals in our country when it comes to providing practical training. Our students have the opportunity to work at these facilities during their vacation and pre-exam internships.

However, the Faculty of Medicine is more than just buildings. First of all, it is the people who work there and the students who study there that make it what it is, today as in previous years. It is the people who founded it and built it together over the decades. Leading experts, doctors, scientists and teachers. Outstanding students and graduates.

The Faculty of Medicine in Hradec Králové has undergone a long and complex journey. During that time, it has become one of the most modern educational and scientific institutions, enjoying high prestige. An integral, solid and indispensable part of Charles University, it has its own specific character and independence, and cooperates with other medical faculties.

Our history binds us together, and we are facing one of the most challenging tasks ahead. We must maintain the current high level of our faculty, whose foundations were laid 80 years ago, and continue to develop its mission, and all its responsibilities in the coming decades.

Structural and Functional Determinants of Oxygen Transport in Exercise: The Role of Total Hemoglobin Mass

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ABSTRACT

Cardiac hemodynamics during exercise depend on both structural and functional adaptations of the oxygen transport system. This narrative review summarizes the knowledge on total hemoglobin mass (tHbmass) as a structural determinant of convective oxygen transport, and cardiac output and hemodynamic responses as key functional determinants, with attention to sex-related differences and clinical translation. We describe carbon monoxide rebreathing as the preferred method for quantifying tHbmass, outline typical values in untrained and endurance-trained men and women, and discuss the contributions of genetics, training, altitude exposure, and blood manipulation to inter-individual variation. The association between tHbmass and maximal oxygen uptake, its sport-specific distribution, and emerging clinical applications in the differential diagnosis of anemia and risk stratification are highlighted. We then review the regulation of cardiac output and arteriovenous oxygen difference during dynamic exercise, compare invasive and noninvasive techniques for their assessment, and summarize consistent sex differences in stroke volume, cardiac output, blood volume, and oxygen-carrying capacity. Across both domains, major gaps remain, particularly in the paucity of data in women and elite athletes studied at or near their physiological limits. Integrative assessments combining tHbmass, blood volume, and exercise hemodynamics may improve the understanding of both normal performance and cardiovascular pathology.

KEYWORDS

cardiac output; total hemoglobin mass; exercise; woman; elite athlete; man; oxygen transport systems

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INTRODUCTION

The total hemoglobin mass (tHbmass) represents the total amount of hemoglobin in circulation and is a key determinant of blood oxygen-carrying capacity. Unlike hemoglobin concentration (Hb), which can be influenced by plasma volume changes, tHbmass directly reflects the oxygen transport potential and correlates strongly with maximal oxygen uptake (VO_2max) and endurance performance (12, 13). An increase of 1 g in tHbmass is estimated to raise VO_2max by ~4 $mL \cdot min^{-1}$ (12). Elite endurance athletes have substantially higher tHbmass than untrained individuals – on average about 35% greater – enabling superior aerobic performance (10, 14). This expansion can be even more pronounced (by an additional ~14%) in athletes native to high altitude (e.g. ~2600 m) (15, 16). In contrast, hemoglobin concentration alone often fails to distinguish athletic adaptations, as endurance athletes typically expand plasma volume such that (Hb) remains within the normal range despite elevated tHbmass (10). Indeed, numerous studies have confirmed a strong relationship between VO_2max and tHbmass or blood volume, whereas (Hb) is a poor predictor of aerobic capacity (12). These observations underscore the importance of tHbmass as a more physiologically relevant marker of oxygen transport in sports hemodynamics. This chapter reviews the methods used to measure tHbmass, the physiological underpinnings and variability of tHbmass, and its applications in athletic and clinical contexts, following a systematic and evidence-based approach.

MEASUREMENT TECHNIQUES

Determining tHbmass requires measuring the total circulating hemoglobin, which can be achieved through dilution techniques. Historically accepted gold standards involved the infusion of tracers (e.g. radioisotope-labeled erythrocytes for red cell volume and albumin for plasma volume) (17). However, tracer methods are costly and invasive, making them impractical for routine use. In sports and clinical research, the carbon monoxide rebreathing method has become the preferred technique for measuring tHbmass, owing to its accuracy comparable to radioactive methods and minimal health risk (15, 18, 19). The principle, introduced by Haldane in 1900, is to inhale a small dose of carbon monoxide (CO) mixed with oxygen and rebreathe it in a closed circuit for a short period. CO has a high affinity for hemoglobin; thus, a known quantity of CO binds to a proportion of the circulating Hb. By measuring the increase in carboxy hemoglobin (%HbCO) in the blood before and after rebreathing, the total Hb Mass can be calculated using the dilution principle. In essence, the absorbed CO dose and the change in %HbCO allow computation of tHbmass, given the known CO–Hb binding capacity and molecular weight of hemoglobin (15, 18). This method has been refined over decades and is now highly reliable when proper protocols are followed. It has been validated against isotope dilution with a very high correlation and has been shown to detect even small changes in blood volume (17, 20). Because only a few milliliters of blood are sampled and CO doses are low, the procedure is safe and well-tolerated, enabling widespread application in both athletes and patients (15, 19).

PROTOCOL AND ADVANCES

Traditional CO rebreathing protocols require approximately 10 min of rebreathing a $CO–O_2$ gas mixture and multiple blood samples. Newer optimized protocols have dramatically shortened this procedure. Schmidt and Prommer introduced a 2-minute CO bolus rebreathing method that yields tHbmass values equivalent to the longer protocol(18). In this optimized method, a bolus of CO (usually ~1.0–1.5 $mL \cdot kg^{-1}$ body weight of CO gas) is inhaled and rebreathed for only 2–3 minutes, which accelerates CO uptake and distribution. Blood is obtained a few minutes before and after rebreathing to measure %HbCO. The shortened protocol was shown to produce virtually identical tHbmass results to the 10-minute method, with a typical error of ~1.7% and narrow limits of agreement (18). Importantly, such precision is sufficient to detect physiologically relevant changes; for example, a ~1.5–2.0% increase in tHbmass can be reliably identified above technical error (15, 16). The optimized CO rebreathing test has a minimal impact on the subject's well-being, aside from a transient slight reduction in maximal exercise capacity immediately after the test due to a small residual CO load. Overall, recent methodological advances have made tHbmass measurement faster and more feasible for routine and repeated testing (15).

BIOLOGICAL SIGNIFICANCE

tHbmass fundamentally determines the oxygen transport capacity of blood. Cross-sectional studies have demonstrated that top-endurance athletes possess markedly greater tHbmass relative to body size than non-athletes, often in the range of ~13–16 g of hemoglobin per kg body weight ($g \cdot kg^{-1}$) for elite males, compared to ~9–11 $g \cdot kg^{-1}$ in untrained men. (Females generally have ~1–2 $g \cdot kg^{-1}$ lower values than males of similar training status owing to lower testosterone and higher iron losses.) For instance, highly trained male endurance athletes average ~13.5 $g \cdot kg^{-1}$, whereas untrained males are ~10 $g \cdot kg^{-1}$. This difference of ~35–50% in tHbmass between elites and untrained individuals is a major contributor to the superior VO_2max of athletes (7, 8, 13, 21). Such a large tHbmass expansion cannot be explained by hemoconcentration; in fact, endurance training triggers plasma volume expansion that keeps (Hb) within the normal range, masking the true increase in oxygen-carrying capacity (10, 13). Thus, measuring tHbmass provides deeper insights into an individual's aerobic potential that hemoglobin concentration alone would miss.

TRAINABILITY AND ALTITUDE

There is an ongoing debate on the extent to which tHbmass can be augmented by training versus genetic

determination. Long-term athletic training at sea level appears to have only a modest effect on tHbmass once initial adaptations are complete (22). In well-trained adults, tHbmass tends to plateau, suggesting a genetic ceiling for everyone (22, 23). A controlled cross-sectional analysis found that 16-year-old competitive endurance athletes had significantly lower tHbmass (~12.4 $g \cdot kg^{-1}$) than 21-year-old athletes (~14.2 $g \cdot kg^{-1}$), but there was no further increase by age 28 despite continued elite training (24). These findings imply that substantial gains in tHbmass occur during late adolescence with intensive training, but additional years of high-level training do not further boost tHbmass in adulthood. As a result, high tHbmass in elite adult athletes is likely to reflect both training during developmental years and innate predisposition. Endogenous erythropoietin stimulation from hypoxic exposure is one of the few potent stimuli that increase tHbmass beyond normal training effects. Altitude exposure (e.g., living high at 2000–2500 m for >14 h/day while training low) typically elicits a 4–8% increase in tHbmass over ~3–4 weeks (15, 22). A meta-analysis-like synthesis in this area suggests an average ~6.5% tHbmass gain after ~3 weeks above 2500 m. This boost, while meaningful, often does not completely bridge the gap to athletes who grew up at altitude in American Ands (who inherently have ~14% higher tHbmass) (15, 16). Contrary to this finding, Kenyan elite runners have similar tHbmass to European low landers, brining different root causes of the dominance of Eastern African runners in endurance running events (25). However, altitude training or simulated hypoxia remains a widely used strategy for stimulating erythropoiesis in athletes. Conversely, under normoxic conditions, true increases in tHbmass are slow and limited, and one study concluded that prolonged sea-level endurance training yields only minor changes in tHbmass, reinforcing that exceptionally high tHbmass in elite athletes is largely genetic or reliant on hypoxic exposure (22). Notably, exogenous erythropoietin (EPO) doping or blood transfusions can artificially elevate tHbmass well beyond an athlete's natural baseline, significantly enhancing oxygen delivery (16). This has implications for both the performance and anti-doping efforts, as discussed below.

ACCURACY AND PRECISION

Achieving high precision in tHbmass measurement is critical, especially for tracking small changes (e.g., due to training or doping). The typical analytical error (coefficient of variation) of modern CO rebreathing is approximately 1–2% when standardized protocols are used (18, 20). Rigorous attention to methodological details can further reduce the errors. For example, using a multi-wavelength co-oximeter to measure %HbCO, researchers recommend taking multiple replicate measurements on the blood sample (e.g., ≥5) and ensuring that the administered CO dose raises %HbCO by at least 5–6% above the baseline (26). Under these conditions, the technical error becomes very low, and a change above ~1.5% in tHbmass can be regarded as real (exceeding the typical error) (20). The CO rebreathing method itself is highly accurate if there are no errors in dosing or sampling, and any deviation in the results is more likely due to technical issues (e.g., leaks in the system, errors in CO volume, or spectrophotometer variability) than to the method principle. Comparisons between CO rebreathing and direct RBC mass measurements showed virtually no systematic bias (17). Thus, when proper calibration, dosing, and replicates are in place, tHbmass can be measured reproducibly for both individual monitoring and research purposes.

REFERENCE VALUES

A robust body of data now defines normal tHbmass ranges. Table 1 summarizes the classification ranges for tHbmass (normalized to body weight) in healthy men and women from untrained status to elite endurance athletes. These values, derived from a large dataset of ~1000 measurements, illustrate the spectrum of tHbmass in relation to athletic proficiency (21).

Tab. 1 Classification of total hemoglobin mass (tHbmass) relative to body weight in endurance athletes vs. untrained populations. Values are typical ranges; "highest recorded" denotes the extreme high values documented in the authors' dataset (21).

Category	Male tHbmass ($g \cdot kg^{-1}$)	Female tHbmass ($g \cdot kg^{-1}$)
Untrained (normal)	9.5–10.5	8.5–9.5
Recreational athlete	10.5–12.0	9.5–10.5
Regional-level athlete	12.0–13.5	10.5–11.5
National elite	13.5–15.0	11.5–12.5
International elite	14.5–6.5	12.0–13.5
Highest recorded	~20.1	~14.5

These ranges show that even within endurance sports, substantial variation exists. For example, an international-class male endurance athlete often has around 15 $g \cdot kg^{-1}$, whereas an untrained man is around 10 $g \cdot kg^{-1}$. Women's values are roughly 1–2 $g \cdot kg^{-1}$ lower in each category. Notably, tHbmass is strongly linked to fat-free mass as well – expressing tHbmass per lean mass can reduce differences between groups, since endurance athletes tend to have less body fat (8, 13). Nonetheless, the absolute tHbmass is a decisive factor for aerobic power. These reference data are useful in both sports science (to gauge if an athlete's tHbmass is commensurate with their competition level) and in identifying aberrant values that might indicate blood manipulation (16).

ATHLETIC APPLICATIONS

In high-performance sports, tHbmass measurements are used to monitor the effects of training interventions or altitude camps. It is thought to be suitable for potential blood doping; however, different approaches have been adopted by the World Antidoping Agency for various reasons (27, 28). A practical application is tracking an athlete's tHbmass before and after an altitude training camp. For instance, a 3-week camp at a moderate altitude might

increase tHbmass by several percent, and measuring this change can confirm whether the athlete responded as expected (15). In one analysis, only 56–69% of athletes showed a meaningful tHbmass increase after altitude exposure, partly due to individual variability in erythropoietic response (29). Understanding such responses can help coaches personalize altitude training strategies. tHbmass data are also valuable for anti-doping programs. The Athlete Biological Passport (ABP) currently monitors indirect markers [hematocrit (Hb), reticulocytes], but tHbmass has been proposed as a more direct indicator of blood manipulation. Research has shown that using tHbmass in testing could enhance the detection of blood doping, since an artificial boost (via EPO or transfusion) would elevate tHbmass outside an athlete's individual baseline range (16). Apart from doping control, another application is talent identification and athlete development. Since a large tHbmass is advantageous for endurance performance, some have speculated that measuring tHbmass in youth athletes could help predict future potential (23). However, as Steiner and Wehrlin observed, 16-year-old athletes had not reached adult tHbmass levels and there was high overlap with non-athletes, suggesting caution in using tHbmass alone as a talent predictor. However, exceptionally high tHbmass values in mature athletes are often indicative of an extreme endurance phenotype or specific adaptation (e.g., altitude), and such data can inform the training focus or the need for medical evaluation if values are anomalously high (24).

In terms of sport-specific variation, endurance disciplines generally show the highest tHbmass. A 2013 study of athletes across different sports found that elite endurance athletes (long distance runners, cyclists, triathletes, cross-country skiers, etc.) all had similarly high relative tHbmass (~13 $g \cdot kg^{-1}$ in males, ~10–11 $g \cdot kg^{-1}$ in females), whereas power-oriented athletes had significantly lower values. For example, elite male judo athletes were measured at ~11.2 ± 0.7 $g \cdot kg^{-1}$, comparable to untrained men, despite their highly competitive level (13). Such findings indicate that a high tHbmass is not a prerequisite for success in purely anaerobic or mixed sports such as judo, and training in those sports does not stimulate large hematological adaptations. On the other hand, sports with a major aerobic component consistently show elevated tHbmass; even among endurance athletes, subtle differences can exist (e.g., professional road cyclists tend to have slightly higher mean tHbmass than swimmers or triathletes) (7, 8). This sport specificity reflects the differing demands and training stimulus; sustained endurance training and high cardiac outputs appear necessary to maximize erythropoiesis and blood volume. Thus, tHbmass measurement allows objective comparison of hematological fitness across sports and can aid in identifying whether an athlete's blood profile is in line with their sport's demands.

CLINICAL APPLICATIONS

Beyond athletics, tHbmass assessment has emerging clinical relevance, particularly in the evaluation of anemia and cardiorespiratory fitness. Traditional anemia diagnosis relies on hemoglobin concentration; however, this can be misleading in conditions where the plasma volume is abnormal. Measuring total hemoglobin directly can distinguish between true anemia (reduced total Hb) and "dilutional" anemia (normal total Hb with expanded plasma volume) (30). Otto et al. demonstrated this in patients with chronic heart failure and liver disease. Despite low hemoglobin concentrations, many of these patients had near normal tHbmass; their low (Hb) was largely due to excess plasma volume. In heart failure patients, tHbmass and (Hb) were poorly correlated, whereas plasma volume explained the variance in (Hb) much better (10). Some individuals with identical tHbmasses were classified as "anemic" or not anemic solely based on fluid volume differences, meaning that conventional labs can lead to misdiagnosis and potentially inappropriate therapy. For example, a patient with a normal total Hb level could appear anemic if they are hypervolemic, potentially prompting unnecessary investigations or iron/EPO therapy, when the real issue is fluid management. By measuring tHbmass (via a quick CO rebreathing test), clinicians can gain clarity: if tHbmass is normal, efforts can focus on reducing plasma volume overload rather than stimulating erythropoiesis. Given that the CO rebreathing method is now simple, safe, and inexpensive, the authors have advocated for its routine use in hospital settings to improve anemia assessment (10).

Another clinical application is in preoperative evaluation and critical care. The total Hb mass has been found to correlate with objective exercise capacity. In pre-surgical patients undergoing cardiopulmonary exercise testing (CPET), tHbmass was significantly associated with peak oxygen consumption, whereas conventional (Hb) did not (10). This suggests that measuring tHbmass could potentially better stratify patients' fitness and oxygen delivery reserve before major surgery, potentially aiding in risk assessment or in guiding preoperative optimization (e.g., deciding on erythropoietic therapy or blood transfusion if tHbmass is truly low). In chronic hemodialysis patients, tHbmass measurements have provided insight into anemia management. A recent study using CO rebreathing in dialysis patients found that most patients had expanded blood and plasma volumes and that their anemia was largely dilutional. Specifically, 18 of the 19 patients met the anemia criterion based on hemoglobin concentration, but when assessed by total red cell volume (a function of tHbmass), only 9 patients had a genuinely low RBC volume (true anemia). The other samples had a normal red cell mass diluted in excess plasma (30). This distinction is clinically important; treatment with erythropoiesis-stimulating agents might be unnecessary or less urgent in patients whose total RBC mass is adequate. Instead, interventions could target fluid removal to correct the hematocrit. These examples illustrate the clinical value of tHbmass measurement in differentiating anemia etiologies and tailoring treatment. As the method becomes more accessible with new devices such as Detalo Clinical (Detalo Health, Denmark) and standardized protocols are being developed, we are likely to see broader adoption in both sports medicine and clinical medicine to assess hemoglobin mass as a vital sign of oxygen transport capacity (15, 30, 31).

HEMODYNAMICS AND EXERCISE

GENERAL DESCRIPTION OF HEMODYNAMICS DURING EXERCISE

During dynamic exercise, the cardiovascular system undergoes profound adjustments to meet the increased metabolic demands of working muscles. Cardiac output increases dramatically and approximately linearly with oxygen uptake (VO_2) (32). In healthy individuals, an increase in cardiac output of approximately 5–6 L is required for each 1 L increase in VO_2 above rest. This robust linear relationship holds across age and fitness levels, with trained athletes capable of raising cardiac output up to 5–6 times resting levels, and in concert with increased oxygen extraction, achieving a 12-to 18-fold increase in oxygen delivery to tissues (33). For example, an untrained male might raise cardiac output from ~5 L/min at rest to ~20–25 L/min at maximal exercise, while simultaneously increasing the arteriovenous O_2 difference (a-v O_2 diff) threefold (e.g. from ~5 to 15 mL O_2 per 100 mL blood), enabling VO_2 to rise from ~0.3 L/min at rest to ~3.0 L/min or more at peak effort. In trained endurance athletes, cardiac output can reach 30–40 L/min, highlighting the extraordinary capacity of the heart to augment the flow during exercise (3).

The increase in cardiac output is mediated by increases in both heart rate and stroke volume. The heart rate increases linearly with the workload. Stroke volume also increases, especially from rest to moderate intensities, owing to enhanced venous return (muscle pump and venoconstriction increasing preload) and augmented myocardial contractility (sympathetic inotropy). In untrained individuals, stroke volume may plateau at approximately 40–50% of VO_2max as the filling time shortens at high heart rates (3). However, in highly trained subjects, stroke volume can continue to rise or at least be maintained up to maximal exertion, owing to cardiac remodeling and superior diastolic function. The net result is that cardiac output ($\dot{Q}$) increases approximately linearly with VO_2, maintaining a ratio of ~5–6 L blood per 1 L O_2 in normoxic exercise (33). This coupling ensures adequate oxygen transport to active muscles.

Peripheral vascular adjustments are accompanied by central cardiac response. Systemic vascular resistance decreases substantially during exercise because of metabolic vasodilation in contracting muscles. Large muscle mass exercises (running, cycling, etc.) trigger an expansive dilatation of arterioles, which can reduce total peripheral resistance to a quarter of resting values. Arterial blood pressure is usually maintained or even elevated during dynamic exercise owing to the feed-forward and reflexive cardiovascular control mechanisms that simultaneously increase cardiac output to offset the drop in resistance. The mean arterial pressure typically rises modestly (e.g., from ~90 mmHg at rest to 110–130 mmHg at peak exercise) despite the large decrease in resistance, indicating that the flow increase is proportionally even greater. The result is a finely tuned cardiovascular response: heart rate and contractility increase (raising cardiac output), vein constriction (augmenting preload), and arterioles in active muscles dilate (lowering afterload), all coordinated to deliver oxygen when needed while maintaining perfusion pressure (3).

It was historically assumed that maximal exercise is primarily "cardio-limited", meaning that the pumping capacity of the heart is the rate-limiting factor for oxygen delivery and VO_2max. Indeed, maximum cardiac output correlates strongly with VO_2max in homogeneous groups, and interventions, such as endurance training or blood doping, that enhance cardiac output generally raise VO_2max (34). However, a large body of evidence indicates that peripheral factors play a critical role in governing circulatory response and exercise capacity (35). The classic work of Guyton et al. demonstrated that the heart cannot increase output unless the peripheral vasculature "allows" it via sufficient venous return and vasodilation, and that the circulation is demand-driven by the muscles (36). Furthermore, Rowland (2005) emphasized that focusing solely on cardiac determinants "may not be appropriate and could cloud our understanding" of aerobic fitness, since peripheral arteriolar dilation and the skeletal muscle pump largely dictate the increase in flow during exercise in healthy individuals (37). In other words, the heart responds to the demands set by the muscles and is a servant to the periphery. Thus, optimal exercise hemodynamics require the integration of central and peripheral adaptations such as a strong heart, adequate blood volume and hemoglobin mass, responsive vasculature, and efficient muscle oxygen extraction. Deficits in any component can limit overall performance.

MEASUREMENT TECHNIQUES OF HEMODYNAMICS DURING EXERCISE

Accurate measurement of hemodynamic variables (particularly cardiac output) during exercise is challenging. Historically, the gold-standard methods were invasive: the Direct Fick method and indicator dilution methods (e.g., thermodilution) performed with cardiac catheters (3). Although invasive techniques can be very accurate, they are clinically and logistically difficult for exercise studies. Consequently, a variety of less-invasive and non-invasive methods have been developed. This section outlines the key techniques and discusses their accuracy and utilization in exercise testing.

INVASIVE REFERENCE METHODS

The Direct Fick method determines cardiac output ($\dot{Q}$) by measuring whole-body oxygen uptake (VO_2) and arteriovenous O_2 content difference. In practice, VO_2 is obtained via metabolic gas analysis, and blood samples are drawn from a systemic artery and mixed venous blood (via a pulmonary artery catheter) to measure O_2 content. Cardiac output was calculated as $\dot{Q} = \frac{\dot{V}O_2}{C_aO_2 - C_vO_2}$ (Fick equation). When performed carefully with measured VO_2 and blood gases, the direct Fick test is highly accurate, particularly under steady-state conditions. Its drawbacks include the need for invasive PA catheterization and technical difficulties during exercise (3).

In contrast, the thermodilution method involves injecting a cold saline bolus into the right atrium and measuring the downstream temperature change in the pulmonary

artery. CO was computed from the thermodilution curve using the conservation of energy principles (2). Thermodilution is widely used in clinical settings (e.g., intensive care) and is convenient for repeated measures at rest. However, it may be less accurate during vigorous exercise owing to factors such as injectate warming and rhythm or valvular issues. Under ideal conditions, both Fick and thermodilution have errors of the order of 5–15% (2). Even in patients, ethical considerations limit invasive hemodynamic exercise testing to special circumstances. As one group noted, "reference methods often require catheterization of the pulmonary artery, which is not only arduous but also associated with risks," motivating the search for alternatives (33).

IMPEDANCE CARDIOGRAPHY (ICG)

Impedance cardiography is a noninvasive method that has gained popularity for exercise testing because it can provide continuous beat-by-beat estimates of stroke volume and cardiac output. The technique implemented in devices such as PhysioFlow (Menatec, France) involves applying electrodes to the thorax to measure changes in electrical impedance with each cardiac cycle. Blood volume changes in the aorta during systole transiently decrease thoracic impedance. By analyzing the impedance waveform, stroke volume can be estimated using proprietary algorithms. Modern impedance cardiographs use improved signal processing (signal-morphology ICG) to better account for motion and artifacts, making them more suitable for exercise conditions (33). ICG is completely noninvasive (just surface electrodes), easy to apply, and can track dynamic changes continuously during exercise. However, accuracy and validation are long-standing concerns. Early studies of older ICG systems showed mixed results; however, newer devices (e.g., PhysioFlow) have been validated against invasive standards in various settings. An important 2015 study by Siebenmann et al. directly compared four methods (modified Fick, inert gas rebreathing, PhysioFlow impedance, and pulse contour analysis) in subjects during incremental cycling in normoxia and hypoxia. They found that all methods detected the increase in cardiac output with intensity, but the absolute values and $\dot{Q}$–VO_2 slopes differed by up to 50% between devices. In normoxia, the "true" slope (by Fick) was ~5 L/min increase in $\dot{Q}$ per 1 L/min VO_2, and the PhysioFlow gave a similar slope (~6 L/min per 1 L VO_2, within the 95% CI of Fick). This suggests that impedance cardiography may provide more consistent and physiologically plausible estimates during exercise than other noninvasive methods (33).

Despite these favorable results, one must consider that impedance cardiography requires careful application and device-specific calibration. Motion artifacts, although mitigated in newer devices, can still pose challenges during high-intensity exercise (especially running or upper-body movement). Legendre et al. (2021) utilized impedance cardiography during cardiopulmonary exercise testing in chronic heart failure and found that peak exercise cardiac output measured by ICG was the strongest hemodynamic predictor of prognosis, independent of VO_2peak (38).

INERT GAS REBREATHING

Another noninvasive approach is inert gas rebreathing (e.g., using the Innocor, Cosmed, Italy). Subjects rebreathe a small volume of a blood-soluble inert gas (such as nitrous oxide) mixed with oxygen for a few breaths. Uptake of the gas by pulmonary blood flow causes its concentration to decrease, and the cardiac output is estimated (applying the Fick principle for inert gas). Rebreathing is appealing because it measures $\dot{Q}$ from gas exchange without blood draws or catheters. It has been validated at rest and during mild exercise against direct Fick and thermodilution, often showing mean differences of <1 L/min. However, during high-intensity exercise, these assumptions can break down. Indeed, Siebenmann et al. found that the Innocor systematically read lower $\dot{Q}$ than other methods at maximal exercise, and more than one-third of the Innocor readings were implausibly low (implying negative venous O_2 content) (33). Thus, inert gas rebreathing is now considered inconvenient for exercise at near-maximal cardiac output.

PULSE CONTOUR METHODS

Pulse contour analysis continuously estimates cardiac output from the arterial pressure waveform recorded at the finger or wrist. It is noninvasive and provides beat-by-beat data. However, it often requires individual calibration (e.g., with blood pressure and demographic data) and can be sensitive to vasomotor changes (which are profound during exercise). For example, Nexfin (Bmeye, Amsterdam, Netherlands) failed to capture an increased cardiac output response during hypoxic exercise (33). The likely explanation is that changes in the vascular tone and pressure waveform shape under different conditions can confound pulse contour algorithms.

HEMODYNAMIC DIFFERENCES BETWEEN MEN AND WOMEN DURING EXERCISE

Men and women exhibit noteworthy differences in cardiovascular structure and function, which translate into distinct hemodynamic responses during exercise. On average, men achieved higher absolute cardiac outputs and VO_2max values than women, even when matched for age and training status (39). These differences are largely attributable to the body size, composition, and sex-related physiological factors.

CARDIAC OUTPUT AND STROKE VOLUME

Women generally have smaller resting and maximal stroke volumes than men. This is partly due to smaller cardiac dimensions (lower left ventricular end-diastolic volume [LVEDV] and myocardial mass) in females. Even when body size is considered, men tend to have a slightly higher stroke index (SV normalized to the body surface area) at rest and during exercise (32). For instance, in one study of young adults matched by fitness, untrained men had a maximal stroke volume ~20% greater than women (e.g., ~120 mL vs. ~100 mL), and even after normalizing to body size, a small gap remained (32, 40). As a result,

Tab. 2 Hemodynamic differences at peak exercise between men and women (32).

Parameter	Men vs Women (peak exercise)
Heart Rate (max)	~No significant difference (age-adjusted)
Stroke Volume (max)	Higher in men (even after size adjustment)
Cardiac Output (max)	Higher in men (men often >20 L/min vs women ~15–20 L/min)
Cardiac Index ($\dot{Q}$/BSA)	Slightly higher in men or similar
Ejection Fraction	Similar or slightly higher in men
Arterio-venous O_2 diff	Higher in men (women extract less O_2)
Systemic Vascular Resistance	Lower in women at equivalent work (more vasodilation)

the maximal cardiac output is usually higher in men. A typical maximal $\dot{Q}$ for a healthy, moderately fit male might be 20–25 L/min, whereas for a female with similar fitness, it might be 15–20 L/min. In a representative study, Diaz-Canestro et al. (2022) found that peak exercise cardiac output (adjusted for body mass) was ~25% lower in women than in men (women: ~13 L/min normalized vs. men: ~17 L/min normalized), corresponding to lower VO_2 Peak values (42 ± 9 vs. 50 ± 11 mL/min) (39). The primary driver of the cardiac output difference was stroke volume, since maximal heart rates were not significantly different between sexes (both typically reached ~85–90% of the age-predicted maximum, and actual max HR values were similar when matched by age). Table 2 summarizes the key hemodynamic differences during peak exercise.

The slightly lower stroke volume in women is not solely due to body size. Studies controlling for lean body mass still find women's stroke volume index to be a bit lower (41, 42), implying intrinsic cardiac or hemodynamic differences. Women's left ventricles are not only smaller, but also their blood volume is ~10–20% lower per body weight on average (7, 21). In a crossover experiment, reducing young men's blood volume and hemoglobin to female levels abolished the previously higher exercise LVEDV, SV, $\dot{Q}$, and VO_2peak of men – making them equivalent to women (39). This elegantly demonstrates that blood volume and O_2 carrying capacity are major determinants of the sex gap in hemodynamics and aerobic capacity.

OXYGEN CARRYING CAPACITY AND EXTRACTION

The arterial O_2 content in woman is ~1–2 mL/dL lower than that in men. At maximal exercise, women also tend to have slightly higher mixed-venous O_2 content (i.e., they extract slightly less of the delivered O_2). The net effect is the smaller a-v O_2 difference among women. Indeed, Bassareo and Crisafulli (2020) noted that the one parameter "unanimously" lower in females is the a-vO_2 diff, due largely to lower hemoglobin and O_2 carrying capacity (32). For example, if a man has a maximal a-vO_2 diff of 15–16 mL/100 mL, a woman with a similar fitness might reach ~13–14 mL/100 mL. This is not because women's muscles cannot extract oxygen as a percentage; rather, if a woman starts with an arterial O_2 content of ~18–19 mL/dL (due to lower Hb) and extracts 80%, her venous content may be ~3–4 mL/dL. A man starting at ~20 mL/dL and extracting 80% would go down to ~4 mL/dL; the relative extraction was similar, but the absolute difference was slightly larger for the man due to the higher starting O_2 content (4). Regardless, when normalized for arterial O_2 content, the percentage O_2 extraction is often comparable or even higher in women, which indicates that their muscles are indeed utilizing available O_2 efficiently. However, in absolute terms, a smaller O_2 content means that the maximal arteriovenous O_2 difference is usually a few mL/dL less than that in men. This compounds the effect of a lower cardiac output on VO_2max. (4, 32, 41, 42).

CARDIAC FUNCTIONAL RESERVE

Women have a smaller cardiac reserve primarily due to structure, but functionally, their ejection fraction (EF) at peak exercise is similar to that of men. In fact, some studies found that women can attain a higher EF at max (since their end-systolic volumes are very small), but others show no significant difference (32). Historically, a contentious point was whether women exhibited an earlier plateau in stroke volume than did men. Some early reports suggested that untrained women plateau at ~50% VO_2max whereas men plateau closer to 90% VO_2max, possibly because of less increase in contractility or more constraints on filling. More recent research controlling for fitness and body size indicates that both sexes can increase stroke volume through near-maximal intensities, especially if exercise is upright and tested personnel are trained. For example, Wang et al. (2019) found that even highly trained female endurance athletes did not show a stroke volume plateau before exhaustion (43). Thus, the paradigm that women have a "less robust Frank-Starling mechanism" is not conclusively supported; when appropriately scaled, women's percent increase in stroke volume from rest to max is similar to that of men, but the absolute volumes achieved are lower.

CONCLUSION

In summary, hemodynamics have been studied extensively from both structural and functional perspectives to the deep level of detailed descriptions of biological processes. However, a global picture combining both approaches is still missing, and there is almost no evidence when counting differences in both sexes. In addition, the majority of the studies were conducted on sedentary or generally

active populations. Data from elite athletes reaching human physiological limits are missing for various reasons. This is a challenging field, which might shed light on the biological principles of human physiology and possibly also pathophysiology, as we see in the early adoption of methods such as total hemoglobin mass in clinical practice.

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Current and Emerging Approaches to Osseointegration Assessment in Dental Implantology: Limitations, Clinical Utility, and Future Directions

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ABSTRACT

This review evaluates existing methods for the measurement of osseointegration, which is the biological mechanism that assures long-term stability of dental implants. Invasive techniques, such as histology and pull-out torque measures, provide direct objective evaluation; however, they cannot be employed clinically due to their invasive nature. Non-invasive methods such as radiographic imaging, resonance frequency analysis, Periotest, and newer methods utilizing ultrasound have been used clinically. These are mainly based on indirect measurements or incomplete measures regarding bone-to-implant contact. Clinical measures of implant osseointegration are often subjective and vary significantly. Research into biochemical blood markers, biochemical markers in peri-implant fluids, and the use of digital technologies associated with decision-making shows promise for generating more personalized assessment outcomes and possibly predictive capacity. Many factors, including implant design, bone density, surgical technique, systemic disease, and others, influence the accuracy of measurement. Future research assessment will likely be based upon the usage of a multimodal protocol (involving mechanical, radiographic, biological, and computational data) so that the oral surgeon will consider all available data to assist decision-making, evaluation, and enhance long-term assessment of implants.

KEYWORDS

osseointegration; dental implants; resonance frequency analysis; biomarkers

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INTRODUCTION

Osseointegration refers to the biological process wherein an implant becomes osseointegrated, allowing for a successful long-term outcome due to its functional connection to bone tissue (1). To assess osseointegration accurately and therefore have a measure of implant stability to aid in a clinician's prediction of the clinical outcome for the patient, osseointegration measurement techniques have evolved since their conception. One should differentiate between implant stability and osseointegration. They are different phenomena. Osseointegration is a biochemical condition characterized by a close structural association between the bone and the surface of an implant (2). Stability, on the other hand, is a mechanical property. Primary stability is the mechanical bonding of the implant to the bone immediately after surgery, whereas secondary stability is the biological process of bone remodeling and biochemical connection to implant (osseointegration) (1, 2). The most urgent stage towards the success of the implant is the transition period between the two phases.

Although the different types of osseointegration assessment techniques have evolved over the years and are clinically relevant for their usefulness, each type has its own unique advantages and disadvantages (3). In Table 1, a brief comparison of various methods, such as level of invasiveness, clinical utility, advantages, and disadvantages, is presented. Information from research on osseointegration has led to the development of addressing difficult challenges associated with immediate-function clinical protocols, which require a detailed understanding of the relationship between implant biomechanics, biomaterials, and early bone tissue response to mechanical loading (4). The use of dental implants in restorative dentistry has radically changed the face of restorative dental procedures, providing a more stable and, in many cases, permanent prosthetic solution for patients who have lost their teeth. Success with the use of dental implants can be attributed to the osseointegration of the implant into the surrounding bone (1, 2, 5–7). The intent of this article is to address how osseointegration is assessed. Clinical protocols in implant dentistry do not generally include an objective and standardized assessment method for osseointegration. As such, current quantitative methods have not been uniformly applied.

The purpose of this narrative literature review is to analyze presently available and former methods of assessing osseointegration of dental implants focused on clinical relevance, limitations, and clinical interpretability. In addition, new biological and digital technologies are also considered as potential adjuncts to future multimodal assessments.

MATERIAL AND METHODS

The chosen narrative review approach for this project enables a holistic analysis of multiple assessment techniques used for assessing osseointegration. The existing body of evidence consists of experimental, clinical, biological, and digital studies that differ in their strengths of study design, outcome measures, and levels of validation. Due to this variance in study types and measures, systematic reviews with quantitative analysis would have limited applicability. Using a narrative review allows for a comparison of different methods used to assess osseointegration, and for discussion of future developments and techniques on osseointegration that do not yet have a sufficient standardization across the available data.

This narrative review integrates contemporary and developing techniques for determining osseointegration of dental implants. The literature was searched through a targeted investigation of PubMed, Google Scholar, and Scopus. A selection of keywords to identify current and emerging techniques in osseointegration assessment, such as invasive/non-invasive, RFA, Periotest, ultrasound,

Tab. 1 Primary reference method; direct BIC visualization.

Method	Invasiveness	Clinical Use	Accuracy/Strengths	Limitations	Key Citations
Histological Analysis	High (destructive)	Experimental only	Primary reference method; direct BIC visualization	Requires implant removal, contraindicated due to its destructive nature	11, 12
Removal Torque Testing	High (destructive)	Experimental	Quantifies anchorage via torque (Ncm)	Damages bone/implant	13, 14
Radiographic Evaluation	Non-invasive	Routine practice	Assesses bone levels (periapical, CBCT)	Subjective, no true BIC	15, 16, 35
Resonance Frequency Analysis (RFA)	Non-invasive	Common in studies/clinics	ISQ score, repeatable	Varies by implant/bone	3, 17
Periotest	Non-invasive	Limited clinical	Measures mobility via damping	Angle-sensitive, variable	3, 18, 36
Quantitative Ultrasound	Non-invasive	Investigational	Sound propagation/bone quality	Lacks standardization	19, 37
Clinical Parameters	Non-invasive	Routine practice	No pain/mobility, low probing depth	Subjective, unquantified	5, 20, 21
Biomarkers (GCF/salivary)	Minimally invasive	Emerging	Real-time remodeling indicators	No standardization	22

biomarkers, digital/AI, with Boolean operators (AND/ OR) used.

This review included publications written in the English language and published between 1977 and 2025. Publications have been evaluated using clinical, experimental, or review methods to assess either invasive or non-invasive approaches to evaluate clinical parameters, biomarkers, or other digital techniques in both humans and animals. This paper excludes case studies, reports, and non-peer-reviewed research, as well as dental implant studies that do not meet the criteria set within this study. To manage the heterogeneity of the studies included in this review, an approach of grouping the studies into 5 thematic domains of study design (invasive, non-invasive, clinical, biochemical, and digital) was taken. Conclusions were drawn based predominately within their respective thematic domains and not via a direct cross-comparison of results. From the original search, a total of 40 papers were selected that provided key information about the limitations, accuracy of measurement, and future development, which provided the background for Tables 1 and 2. The possibility to group the chosen papers based on the five types or themes, which include invasive, non-invasive, clinical, biochemical, and digital, allows the comparative review of the literature. This is a summary of the shift in the literature towards stability-based methods, which are traditional, to predictive and data-driven methods of modeling.

A purposive sampling methodology was employed to identify 40 publications and create a representative sample of the various methods currently being used to measure osseointegration. As the range of studies designed to evaluate osseointegration is inherently diverse, this sample size will provide adequate information to develop themes related to the five major areas of study discussed in this paper (invasive, non-invasive, clinical, biochemical, and digital measurement techniques) and will enable the establishment of thematic saturation to be reached within this sample size. Considerable emphasis was placed on the requirement that each of the publications included in this selected sample contain sufficient data to describe either a limitation in measurement, clinical value, or a new trend regarding the use of technology for measuring osseointegration in order to support the framework for comparison between measurement techniques shown in Tables 1 and 2. Because of the goal of achieving a high standard of evidence and reducing data variance, case studies (individual cases) that were not subjected to peer review were excluded from the initial selection (screening) process. Therefore, the analysis of the selected publications included only the qualitative assessment of empirical and clinical data from validated studies and included the transition from conventional physical measures to computational and biological models being discussed in this paper.

A total of 40 publications were included in this review. Of these, 30 studies focused on specific assessment methodologies (Non-Invasive, Clinical, Digital, Invasive, and Biochemical methods), while 10 provided essential theoretical background and biological foundations.

The first of many steps employed in completing this review was to conduct a qualitative review or assessment of the included studies. In order to provide an adequate framework to interpret the findings of the included studies, evidence has been organized by study design (e.g., experimental animal studies, clinical observational studies, randomized clinical trials and systematic reviews) and evaluated based on methodological transparency, adequacy of the sample size, reproducibility of the outcome, and clinical relevance. This evaluation process allowed classification of the level of evidence as low, moderate or high, based on the design and quality of reporting without using a full tool for assessing risk of bias as the use of such a tool would have been limited in validity due to the large amount of heterogeneity present in the methodologies and outcome measures of the included studies.

RESULTS

All relevant studies were grouped based upon their main theme; should any study include more than one thematic domain, it was categorized into its primary domain as reflected in its methods and conclusions. The horizontal bar chart (Figure 1) was derived from the frequency distribution of all 30 included publications within five core thematic domains (invasive, non-invasive, clinical, biochemical, and digital) based upon the study's primary focus. Consequently, the chart depicts the comparative quantity of study findings for each thematic area, independently from their methodological rigor, and relevance to clinical practice. Numbers depict the quantity of included publications categorized by thematic area (n=30): Non-Invasive Methods (n=9, 30%), Clinical Parameters (n=7, 23%), Digital Innovations (n=6, 20%), Invasive Methods (n=5, 17%), and Biochemical Methods (n=3, 10%). It also illustrates

Tab. 2 Comparison between measurement techniques.

Emerging Technology	Description	Potential Benefits	Challenges	Key References
Quantitative Ultrasound	Measures sound wave speed through implant-bone interface for stability	Non-radiation; sensitive to healing stages	Needs standardization; early validation stage	19, 37
AI-Driven Prediction	Machine learning analyzes radiographs for success trends	Early failure detection; personalized risks	Training and data needs	23–25
Digital Twins	Simulates patient-specific healing outcomes	Scenario testing without invasion	High infrastructure costs	26, 27, 39, 40
Biochemical Standardization	GCF markers like osteocalcin for remodeling	Real-time biological insights	Lack of validated threshold	22

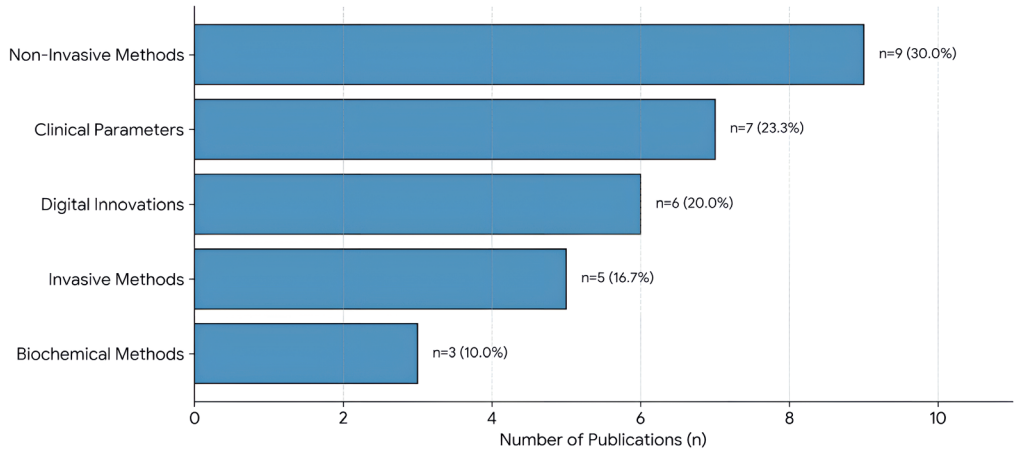

Fig. 1 Distribution of core thematic publications (N=30).

the quantity of evidence found in the literature reviewed, where the majority of the literature focused on noninvasive and digital techniques. Because of this disparity, there is a proportionately smaller number of biochemical papers compared to noninvasive and digital, which indicates that there is not yet sufficient clinical standardization regarding molecular diagnostic procedures, as there are established mechanical and emerging computational techniques. Furthermore, the data extracted from these studies provide information regarding study focus, methodology, main findings, and clinical implications.

Osseointegration is a multifactorial, complex biological phenomenon that starts immediately after the dental implant is placed in the alveolar bone, and the healing cascade (similar to a fracture healing cascade) begins (1, 2). The first inflammatory cells arrive at the surgical site to clear any cellular debris from the tissue and to release cytokines to stimulate the arrival of osteoprogenitor cells (the cell type that produces bone) (8). The next stage of healing is the differentiation biomechanically of the osteoprogenitor cell to an osteoblast, which begins to lay down adapting osteoid and will eventually mineralize into bone (9). In animal study, few weeks after the dental implants are placed, a direct interface occurs between the implant surface and the alveolar bone, described as bone-to-implant contact (BIC) (10). BIC is among the prototypical histological determinants of osseointegration, but it cannot be measured clinically. We will be left with only our surrogates to rely upon in the clinical environment to make osseointegration assessments that include mechanical stability, resonance frequency, or radiographic bone levels.

INVASIVE METHODS OF ASSESSING OSSEOINTEGRATION

a) Histological Analysis

Histology is an objective reference because it supplies photographic records of the bone-implant interfaces (contact points). However, this method necessitates the removal of both the implant and the surrounding bone (11). While the data from histomorphometry is statistically valid as a calculation of the proportion of BIC, it should be considered more of an overall descriptor rather than a measure of performance or effectiveness (12). As with histological techniques, histomorphometric analyses are invasive and include ethical considerations in dentistry. Thus, there are no applications of this method in clinical practice.

b) Removal Torque Testing

The implant removal torque testing, Torque Testing Method (TTM), measures the torque required to unscrew the implant from the bone (13). Higher torque values in Newton Centimeter (Ncm), indicate greater bone anchorage (14). Like histology, it damages the bone and implant. Its primary use is experimental, not clinical. The torque test can interrogate the effectiveness of bone quality, implant design, and surface treatment. The torque test is not used in a routine patient setting.

NON-INVASIVE METHODS OF OSSEOINTEGRATION ASSESSMENT

a) Radiographic Evaluation

In implantology, radiographic images (15) are very common and are simple and non-invasive to obtain. Radiographs, including periapical, panoramic, and cone-beam images, have provided electronic evaluations of the bone level surrounding the implant or other implant-related process. Although marginal bone loss can be identified on radiographic images, as indicated by the change in the bone height surrounding the implant, radiographs do not allow for confirmation of the presence and percentage of bone-to-implant contacts (BIC) surrounding the implant. Radiographs can show changes in marginal bone height, although the presence of connective tissue at the implant surface cannot be identified through these images. Interpretations of radiographs are of a subjective nature (16).

b) Resonance Frequency Analysis (RFA)

Resonance frequency analysis (RFA) is one of the most accepted methods of assessment in implant studies. RFA is accomplished with a device that attaches to the implant. This device creates vibrations in the desirable frequency range through the implant, and the frequency of the sinusoidal pattern of the vibrations is recorded to represent the Implant Stability Quotient (ISQ score). Higher ISQ scores measure stability (17). RFA is a non-destructive method allowing for repeatability and a measure that removes an

aspect of investigator bias. RFA is very useful to monitor the physiological process of bone to implant healing.

c) Periotest

The Periotest device measures damping characteristics and determines the implant's mobility by tapping on the implant and quantifying its damping characteristics (18). For Periotest, a lower Periotest value represents higher stability. However, the Periotest is more sensitive to angulation and positioning than RFA and has more variation than RFA. Other devices for assessing implant stability are also available, including systems based on resonance frequency analysis as well as percussion-based approaches, each with specific methodological limits (3).

d) Quantitative Ultrasound

Ultrasound is demonstrated as a diagnostic tool that measures sound waves traveling through the implant site (19). The speed of sound propagation would indicate bone quality and bone-to-implant contact. Currently, ultrasound has been proposed as safe and potentially useful. It may become one of the options in the future.

CLINICAL PARAMETERS OF OSSEOINTEGRATION

A clinician recognizes the successful fusion of an implant to the bone (osseointegration) by looking for specific clinical signs, which include no pain, no inflammation, and no movement (5). Although there are no standard criteria for assessing osseointegration, these signs can all be used by the clinician to make judgments regarding potential osseointegration.

One additional method of assessing osseointegration is using the probing depth observed around the area of the implant. When probing depth measurements are taken and found to be low without any bleeding, this may help support the possibility of osseointegration having been achieved (5, 20). Proper technique should be utilized during probing to prevent trauma to either the implant or patient.

Percussion sound is another option that clinicians might choose to evaluate osseointegration. Percussion sounds can be evaluated by tapping on the implant with a metal instrument to produce sound, giving some indication of osseointegration status based on the sound produced. If the implant produces a sharp, high-pitched sound when tapped, this may be an indication that osseointegration has occurred. If tapping produces a low-pitch or dull sound, it may indicate that the implant does not support adequate stability and has not fused (integrated) with bone (21).

BIOMARKERS AND MOLECULAR INDICATORS

Biochemical markers are also a recent focus of research. Biochemical markers are proteins found in the products of crevicular fluid that can suggest bone activity. Biomarker studies are focusing on markers, such as osteocalcin, alkaline phosphatase, and interleukins. When possible, localized and relatively non-invasive methods of collection, such as salivary or gingival crevicular fluid (GCF), if the product of the implant, could provide insight into real-time bone remodeling (22). However, a lack of standardization presents a challenge, and clinical use is nonexistent currently.

DIGITAL INNOVATIONS

Artificial intelligence (AI) enhances healthcare diagnostics. In implantology, AI provides analysis of radiographs and predictive abilities for healing and bone density trends (23–25). Machine learning algorithms can predict trends of success associated with implants, in addition to the various types of radiographic options from multiple manufacturers today. Digital workflows allow for the development of 3D models of the patient's cortical bone. These models allow for the determination of stress distribution and osseointegration, providing assistance over time. Potentially in the future is to have patient "digital twins" that may rely entirely on digital and model workflow (26).

An individual's digital twin is a digital representation of a person's medical history, a digital copy of the actual patient, constructed from a combination of detailed patient records and various other aspects of the person's health status. In essence, this virtual replica of the individual allows simulation, forecasting of outcomes, and tailoring of therapies in a way that closely represents the patient themselves. The idea has been adapted from engineering to allow better applications within the field of personalized medicine (27).

DISCUSSION

Evaluation of osseointegration is undoubtedly one of the most important clinical issues for all forms of implant dental procedures. Multiple variables can impact measurement. For example, implant type and materials, surface properties, bone density, and operative technique. Patient factors such as smoking, uncontrolled diabetes, osteoporosis, and vitamin D deficiency are all variables that can impact osseointegration. Measurement figures should account for all of these variables in order to obtain reliable values (28–31). The future is multifactorial. Radiographs, RFA, biomarkers, and computer modelling when used collectively will account for all potential measures and provide a holistic view of the process. Personalized medicine will likely play a more dominant role (32). Patient-specific risk profiles or timelines with risk determinations assessed through artificial intelligence enhancement could direct clinicians on treatment timelines and reduce overall adverse events while improving functional outcomes (23–25). Research should seek to standardize procedures. A standardized protocol can facilitate comparison between studies and clinical implementations.

Although researchers have conducted numerous studies regarding osseointegration, there is no available clinical method that offers a definitive and thorough understanding of the biological and mechanical components of bone-to-implant attachment. The following are four key findings from the body of evidence reviewed here, indicating that, despite being helpful in some situations, current

diagnostic techniques fail to provide complete and reliable information in a wide variety of clinical scenarios (33, 34). Evidence strength varies significantly based on the assessment modalities used in the evaluation of mechanical stability. Clinical validation for mechanical stability tools, such as radiographic assessment and RFA, is robust, while evidence of clinical validity for biochemical markers and AI predictive systems is mostly from developing or exploratory studies; thus, limiting their ability to make clinical generalizations.

Although invasive methods like histological assessment and removal torque are evident experimentally, they cannot be applied in clinical practice since they are destructive and unethical in the clinical practices (11, 12). The direct measurements obtained from these processes can only be used for research experiments since this type of information is not available for in vivo studies (13). These techniques primarily serve to validate indirect measures, but they do not currently play a significant role in the everyday practice of clinicians.

Radiography is a widely used non-invasive assessment technique. It only provides inferences, at best (usually marginal bone levels), without ever informing us of true osseous contact at the interface with the implant. Further, radiographs are subjective, and their usefulness as a diagnostic tool is limited without comparative images or clinical follow-up (15, 16). Cone-beam computed tomography (CBCT) offers higher spatial resolution. However, the fact that it comes with costs and radiation exposure, and that it does not clearly show soft tissue pathology or true soft tissue-implant connection, limits its diagnostic value (15, 35).

Resonance Frequency Analysis (RFA) with its metric Implant Stability Quotient (ISQ) offers reproducible, operator-independent evaluations of primary and secondary stability with many clinical applications (3). RFA and ISQ have entered the clinical decision-making process, particularly in operative protocols or non-removable loading relative to loading decisions. Generally, an ISQ >70 is indicative of high primary stability, providing a clinical value for immediate or early loading protocols. Values ranging between 60 and 70 are considered acceptable for standard loading after a conventional healing period, while an ISQ <60 typically suggests low stability (3, 17, 36). However, ISQ values are not standardized or equal and vary with implant design, transducer calibration, and the bone quality that surrounds the interface. Although Periotest measures have been made ostensibly similar to ISQ, Periotest success is defined by values ranging from −8 to +5, where lower or more negative values indicate higher stability. However, this method demonstrates higher variability than RFA because measurements are significantly influenced by the vertical position and angulation of the instrument (18, 36).

Quantitative ultrasound, as a novel domain, investigates the acoustic propagation of contact with the bone surface estimation in vivo. In theory, this might be a more sensitive option, and it is certainly safe and practical from a cost perspective. However, the field is currently exploratory. Interpreting valid criteria of standardization and correlating to outcomes has not yet progressed at a level fit for clinical use (19, 37).

The resultant adoption of percussion testing, an older clinical technique reassembled with an acoustic analysis bent, also reflects a broader attempt to identify clinically valuable data from basic, empirical observations. While the sounds produced by a metallic device may provide some qualitative indicators of implant stability, they lack quantification and reliability because they depend on operator reproducibility. As such, its continued existence in clinical practice demonstrates the ongoing demand for methods to evaluate stability that are inexpensive, easy to use, and do not require sophisticated machinery (21, 38).

Molecular and biochemical markers also represent an interesting area. They potentially offer the advantage of inferring osseous activity in real time via peri-implant fluids or serum (22). However, we are not at a point at which we can use those markers as actionable biomarkers within patient populations, because the thresholds are not currently validated, and discrepancies exist between different patient populations. Research has shown that osteocalcin, alkaline phosphatase (ALP), and interleukin-1β (IL-1β) are potential biomarkers found in peri-implant crevicular fluid (PICF) and saliva but currently is not an established clinical threshold universally accepted for immediate surgical or prosthetic intervention. Non-validated data and differing systemic health conditions prevent concentration-dependent fluctuating values from guiding clinicians in their determinations of osseointegration success or failure. Therefore, these markers are only used in research settings. For a biomarker to attain clinical acceptance it must be embedded within a rapid, cost-efficient point-of-care (POC) test that can provide results during the patient visit.

The implementation of Artificial Intelligence in implantology has transformed from being merely a notion to being comprised of an array of scientifically based applications that deliver considerable value in developing diagnostic accuracy. Currently, a technique has been validated for the automated identification and numbering of dental implants from panoramic radiographs, thus reducing human error associated with the documentation of clinical records (24, 25). In addition, machine learning algorithms and radiomics techniques are issued for the analysis of bone density and quality derived from CBCT scans (23). Thus, producing objective, quantitative data for practitioners to use when developing surgical plans. Although these tools are currently being used as a supportive decision-making tool, rather than as independent diagnostic devices, they provide a statistically modified data methodology for estimating the probability of an individual's long-term success in implant therapy and for customizing treatment protocols.

Digital innovation has the greatest potential to disrupt the status quo going forward. The integration of AI and advanced analytics of diagnostic imaging and longitudinal datasets, or workflow-based assessment tools like surgical planning diagnostics, offers clinical solutions never before possible (23–27, 39, 40). Even as hypothetical concepts, "digital twins", which involve simulation modeling based on multimodal data of a virtual patient, may allow clinical users to digitally simulate predicted implant capability or clinical performance (26, 27). However, like any

new technology, the value of these new predictive digital assessment or simulation methods is largely dependent on infrastructure, data flow, data interoperability, and clinician user training. If small practices cannot integrate these new digital products directly into workflows to maximize efficiencies in healthcare delivery, then generalizability will become limited to individual practitioners or academic and specialized centers (39, 40).

Implant geometry, surgical method, bone density, systemic health, and loading regimes will all affect the accuracy and interpretation of measurement. Therefore, both qualitative and quantitative assessments integrated with clinical (mixed models with whole patient assessments) will be optimal, where it could be realized using various methods that include mechanical testing, radiographic imaging, biochemical monitoring, and computational modeling methods to create a more comprehensive dynamic understanding of osseointegration over time. A goal is to inform, not to replace clinical decision-making.

Future studies should not only emphasize improved technology, but also the methodology for calibrating technology and standardize the processes when possible. If we can harmonize the measuring schemes, calibrating protocols, and reporting outcome definitions, we may preserve the integrity of the clinical trials and accelerate the transfer of new technology into the clinic. Biological (secondary) stability assessment remains the clinical benchmark for implantology. The combination of biological and computational monitoring is the next frontier in the field. Otherwise, we will continue assess osseointegration largely on the basis of concept and not precise measurements. The characteristics, advantages, and challenges associated with these emerging technologies are summarized in Table 2.

CONCLUSION

Assessment of osseointegration remains difficult due to the absence of a consistent technique to detect osseointegration, with many different ways of measuring it all having their own benefits and drawbacks. Decisions about how to treat patients based on assessment of osseointegration usually involve combining multiple measurement types. With advances in technology, there exists the opportunity for future non-invasive, accurate assessments of osseointegration, as more will be learned about biology and biomechanics, which will allow for more confidence in the reliability of assessments of osseointegration. The more improved our measurement techniques for osseointegration are, the more improved care will be available to patients. Therefore, better measurements provide patients with greater certainty regarding the safety, security, and durability of the implant supra-structure.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Managing Impacted Mandibular Third Molars: A Scoping Review of Surgical Extraction versus Orthodontic Traction and Nerve Injury Risk

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ABSTRACT

The management of impacted mandibular third molars can be a difficult clinical issue due to the proximity of the tooth to critical neurovascular structures. Surgical removal is routinely performed, but the technique carries a known risk of injury to the inferior alveolar and lingual nerves. The complication may induce temporary or permanent sensory impairment. Orthodontic traction can be an alternative to reposition the tooth in a more desirable location before surgical removal. The selection of the appropriate treatment is important to avoid a mechanical injury and to allow the adjacent bone and soft tissue to adapt, which may reduce the risk of nerve injury from compression or transection. This review discusses the anatomy of the inferior alveolar canal and the lingual nerve route, describes the known mechanisms and classifications of nerve injury, and outlines how orthodontic traction may diminish these risks. Technical aspects of traction, including the surgical exposure with coronectomy or not, force application, anchorage methods, and radiographic observation, are reviewed. Potential complications, including root resorption and unwanted tooth movement, were also explained. Criteria for patient selection are discussed, with emphasis on age, root morphology, eruption space, and imaging findings that indicate proximity to neurovascular structures. The purpose of this scoping review was to compare orthodontic traction and complete surgical extraction of mandibular impacted third molars with respect to injury of the inferior alveolar nerve (IAN) and lingual nerve (LN).
The limited but growing evidence allows us to identify gaps in long-term outcome data and calls for further prospective studies. Orthodontic traction cannot replace extraction in every case, but for carefully chosen patients, it may offer a practical treatment option for preserving neurosensory function. The approach requires interdisciplinary collaboration, precise biomechanical planning, and a clear explanation of treatment goals to support informed decision-making.

KEYWORDS

impacted third molar; orthodontic traction; inferior alveolar nerve; lingual nerve; coronectomy; surgical extraction

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INTRODUCTION

Impacted mandibular third molars are concerned in both orthodontic and oral surgery practice with various frequency. These teeth often remain impacted because of space limitations and unfavourable angulation. According to the literature, these teeth may contribute to pericoronitis, caries of adjacent teeth, topical periodontitis, and cystic change, requiring conservative or surgical intervention (1, 2, 3).

Surgical extraction is effective but has potential complications. Injury to either inferior alveolar nerve or lingual nerve can result in altered sensation of the lower lip, chin, tongue, and floor of the mouth. The sensory alteration can vary from temporary to permanent (4, 5).

An alternative treatment option may be orthodontic traction. Orthodontic traction is the process of applying a controlled force to the impacted tooth to achieve guided eruption. Unlike extraction, orthodontic traction allows for the surrounding bone to remodel and for the tooth to erupt in a continuous, controlled manner that diminishes the possibility of nerve compression or trauma if the case assessed properly (6). Orthodontic traction with coronectomy or not is a technique of main interest in the instance of close contact between the tooth roots and the mandibular canal (7). The previous finding is usually observed during radiological assessment. Successful orthodontic traction relies upon a thorough understanding of the mandibular anatomy. Careful assessment of dental development and three-dimensional imaging are also essential in the treatment plan.

Patients with adequate space for the tooth to erupt, with little root development, are good candidates for orthodontic traction or guided eruption (8). On the contrary, ankylosis, curved root morphology, active infection, and related cystic lesions may preclude orthodontic treatment (9). Anatomical structures of specific importance are the inferior alveolar nerve (IAN) and lingual nerve (LN), which are the principal neurovascular structures adjacent to the impacted mandibular third molars. Detailed anatomical knowledge regarding the IAN and LN is a starting point for any clinician, including orthodontist, to provide evidence-based and ethical care.

The IAN is the terminal sensory branch of the mandibular division of the trigeminal nerve. Entering through the mandibular foramen on the ramus' medial surface, it courses through the mandibular canal, giving dental and interdental branches before emerging at the mental foramen to distribute as the mental nerve (10). The path of the IAN is located in proximity to the roots of the third molar, and in some patients, the canal may be seen superimposed on panoramic tomography or encircle the tooth roots. The nerve provides sensation to the mandibular teeth, the lower lip, and the chin, and injury can result in sensory disturbance across these anatomical areas (11).

Near the third molar, the lingual nerve lies about 2–3mm beneath the mucosa, a position that makes it highly vulnerable during reflection of a lingual flap or removal of lingual cortical bone (12). It supplies general sensation to the anterior two-thirds of the tongue and the floor of the mouth and carries taste fibres via the chorda tympani (13).

The surgical management of impacted mandibular third molars present significant clinical challenges, particularly when radiographic evidence indicates a close relation between the tooth roots and the mandibular canal. While removal is the definitive solution for symptomatic teeth, the risk of iatrogenic injury to the IAN and LN (ranging from temporary paraesthesia to permanent sensory loss) necessitates careful risk-benefit analysis.

Orthodontic traction, including surgical exposure with or without coronectomy, force application, anchorage methods, and radiographic observation, is reviewed and discussed.

The advantages and disadvantages of these techniques are described in Table 1.

Tab. 1 This table outlines the definitive advantages and potential complications of surgical extraction versus orthodontic traction, highlighting the differences in treatment duration and anatomical risks associated with each approach.

Technique	Advantages	Disadvantages
Surgical Extraction	Definitive removal of the impacted tooth.	Risk of inferior alveolar or lingual nerve injury leading to temporary or permanent sensory disturbance.
	Short treatment time once surgery is performed.	Potential for postoperative pain, swelling, and infection.
	Indicated for infection, cystic change, or unfavourable angulation.	Bone removal and nerve proximity increase complication rates, especially in high-risk anatomy.
Orthodontic Traction	Gradual, controlled tooth movement that may lower the risk of acute nerve injury.	Prolonged treatment over months with repeated visits and imaging.
	Allows bone to remodel during eruption.	Possible root resorption, periodontal injury, or migration toward the canal or lingual plate.
	Useful where imaging shows close contact between roots and the mandibular canal.	Requires surgical exposure and stable anchorage.
	Can be combined with coronectomy if roots remain close to the canal.	Attachment failure, infection, or poor oral hygiene can delay or compromise results.
		Limited evidence and lack of long-term comparative data.

MATERIALS AND METHODS

The purpose of this scoping review was to compare orthodontic traction (with coronectomy or not) and complete surgical extraction of mandibular impacted third molars with respect to injury of the inferior alveolar nerve (IAN) and lingual nerve (LN). Given the variability in reported outcomes and the lack of large, standardized studies, a gap in literature exists comparing the consistent estimates of nerve injury risk for each technique. To address this, relevant articles were identified through a structured search of PubMed, focusing on clinical studies, systematic reviews, and meta-analyses that reported rates of IAN and LN injury. Relevant articles were identified, covering a period that includes essential landmark studies as well as the most recent clinical developments. While foundational data were included for historical reasons, the majority of the analyzed evidence, particularly regarding 3D imaging and standardized traction protocols, was derived from a significant body of literature published after 2010. Data from these studies were extracted and analyzed to provide a comparative overview of the two techniques, highlighting both immediate and long-term nerve injury outcomes.

RESULTS

MECHANISMS OF INJURY

Both nerves can be damaged by direct trauma, compression, stretching, or ischaemia (14, 15). Surgical extraction may involve sharp burs, elevators, or retractors that may contact the canal or the lingual plate, leading to neurapraxia or more severe lesions. Orthodontic traction reduces the chance of direct mechanical insults but is not completely risk-free. Excessive orthodontic force or migration of the tooth roots into the canal could produce compressive neuropathy. Likewise, traction that displaces the tooth lingually may increase pressure on the LN, especially if the cortical bone is thin and fracture (16, 17).

In a prospective clinical study of 4338 lower third molar extractions, 0.35% had inferior alveolar nerve (IAN) injury and 0.69% had lingual nerve (LN) injury (18).

In another study of 3236 mandibular third molar extractions, 1.5% inferior alveolar nerve (IAN) sensory loss and 1.8% developed lingual nerve (LN) sensory loss presented at first month. At 18–24 months, permanent deficits were recorded in 0.6% for the IAN and 1.1% for the LN (19).

Iatrogenic nerve injury during the surgical management of impacted mandibular third molars can occur from direct and indirect trauma. Direct trauma happens when surgical instruments or excessive orthodontic force causes mechanical trauma to the inferior alveolar or lingual nerve (20, 21). These could be the result of extraction when there is contact with burs, elevators or retractors that can traumatize or transect the nerve tissue, or the use of excessive orthodontic force that may compress the canal or displace the tooth against the lingual plate (6–8). Indirect trauma can involve other secondary effects such as, compression, and ischaemia (11, 14). Within the confined mandibular canal, a swelling that can happen from within or the migration of the tooth roots during traction can create sustaining compression that reduces blood supply, block conduction (22–24). Commonly, either pathway to the nerve injury can lead to various degrees of paraesthesia, hypoesthesia, or dysaesthesia of the lower lip, chin or tongue (4–12). In most cases, recovery will usually happen overtime, but some changes might persist. This highlights the importance of using imaging to aid assessment, recognizing applied forces or compensatory changes, maintaining appropriate monitored forces and evaluating neurosensory status, as continuous assessments will be important to the treatment (5–10).

CLINICAL MANIFESTATIONS

Injury to the IAN may present as paraesthesia, hypoesthesia, or dysaesthesia of the lower lip and chin. Lingual nerve trauma can lead to numbness of the tongue, altered taste, or burning sensations (4, 5, 11, 15, 18, 23, 24). Many of these sensory changes resolve within weeks, but a proportion persists beyond six months and may become permanent (1–5). Severity is often classified according to Seddon and Sunderland, ranging from transient conduction block, such as neurapraxia and axonotmesis, to complete neurotmesis, each with different prognostic implications (25–27).

Accurate imaging is essential to evaluate the risk of nerve injury. Cone-beam computed tomography provides three-dimensional views of the canal relative to the tooth roots and can indicate the lingual plate thickness (10, 11). Preoperative evaluation of these structures indicate both surgical planning and the design of orthodontic force vectors (4–6). In orthodontic traction, low-magnitude, continuous forces combined with frequent radiographic monitoring can help avoid tooth migration in the canal or displacement to the lingual plate (16).

Protection of the IAN and LN should be regarded as of primary importance when planning any intervention for impacted mandibular third molars (4, 14). The slow, controlled movement achieved through orthodontic traction may reduce the likelihood of acute nerve injury compared with immediate extraction, provided case selection and biomechanical control (6–8). However, the possibility of delayed or progressive nerve disturbance remains, underscoring the need for informed consent, and regular neurosensory evaluation.

ORTHODONTIC TRACTION TECHNIQUE

Orthodontic traction may be used (with coronectomy or not) to move an impacted mandibular third molar gradually into a position that permits functional eruption or simple extraction (7, 28). The orthodontic principles of light and continuous force application require adjustments according to the tooth's location, the density of mandibular bone, and the proximity of vital structures (20).

Clinical examination evaluates mouth opening, periodontal health, and adjacent tooth condition. Cone-beam computed tomography (CBCT) is used to evaluate the relationship of the third molar roots to the mandibular canal and to assess the thickness of the lingual plate (16). Panoramic radiographs alone may not always provide the

details needed for safe planning, especially if the roots of the third molar are superimposed on the IAN (22, 28). The ideal candidate for orthodontic traction is usually a younger patient with incomplete root formation, sufficient eruption space, and no signs of ankylosis or cystic changes (9). A clear written consent form is essential, because treatment often extends over several months and demands repeated follow-up visits.

The crown of the impacted tooth must be surgically uncovered to allow placement of orthodontic appliances. A conservative flap design is preferred to preserve gingival keratinized tissue and maintain good blood supply. Bone removal may be limited to what is required for visibility and bonding of the attachment (9, 20, 29, 30). This condition may be described as minor surgical orthodontics.

Once the crown of the tooth is exposed and isolated, an attachment such as a bonded button or bracket is bonded to the enamel. Traction forces can be delivered with chains, nickel-titanium coil springs, or ligature wires (16). The choice of the eruption technique depends on the eruption path. Force levels are kept light to permit physiologic bone remodeling and to reduce the risk of root resorption or nerve compression (20).

Anchorage is essential to direct the movement of the impacted tooth while preventing the displacement of adjacent teeth. Options include fixed orthodontic appliances on adjacent teeth, a rigid lingual arch, or temporary anchorage devices (TADs) inserted into cortical bone such as mini implants or fixation screws (29). Bone fixed anchorage often provides the most stable support in the posterior mandible, particularly when second molars are not suitable as anchorage units (30).

The direction of the orthodontic force should be applied to facilitate a path of eruption that allows the tooth to avoid compressing on the inferior alveolar canal and the lingual plate. Traction is usually planned in a way to move the crown occlusally and buccally, away from the canal (6, 7, 28). Orthodontic traction should be applied once its path of eruption has been planned using cross-sectional radiography to allow appropriate consideration of the location of the tooth in relation to the inferior alveolar nerve canal (10). In order to utilize orthodontic forces correctly, periodic assessments are necessary. As well as, clinical and radiographic assessment to monitor progress and check for potential complications (20). Cone Beam Computed Tomography (CBCT), periapical x-ray, or panoramic tomograph will determine whether the tooth is moving along the planned eruption path, while also ensuring mechanical pressure is not being applied to the canal or excessive root resorption is not occurring (7, 16, 22). Neurological assessment of the lower lip, chin, and tongue should be performed at each appointment to assess changes in sensory perception (4, 5, 11, 15, 18, 23). In situations where the tooth roots are close to the canal, surgical coronectomy can be planned and completed with orthodontic traction (7). Surgical removal of the crown while keeping the roots, will allow eruption of the segmental roots under controlled orthodontic forces, allowing the residual root structures to act as the anchorage unit (6, 9, 28).

In a recent article, coronectomy is suggested to reduce the risk of inferior alveolar nerve injury in comparison to surgical extraction (31). In another relevant paper, the authors concluded that coronectomy could be a safe alternative for teeth in close contact with the nerve when careful case selection and follow-up are applied (32). In a systematic review of 2087 coronectomy procedures, successful coronectomies had nerve injury in 0.5% (inferior alveolar nerve) and 0.05% (lingual nerve). In failed coronectomies, IAN injury rose to 2.6%. Permanent paraesthesia was 0.05% after successful coronectomy and 1.3% after failed coronectomy (33). In a clinical and radiological study of 231 coronectomy cases (mean follow-up 5.7 years), 1.3% developed inferior alveolar nerve (IAN) injury (34). In a retrospective study of 124 coronectomy patients, 4.3% experienced inferior alveolar nerve (IAN) injury as a short-term complication, and 3.5% had IAN injury at long-term follow-up (>3 months) (35).

DISCUSSION

Currently, the extraction of impacted mandibular third molars presents a significant clinical situation, especially when the risk of iatrogenic inferior alveolar or lingual nerve trauma exists. Surgical extraction is the most common treatment approach and has a well documented risk for temporary or permanent sensory disturbance (4–7, 11, 18, 19). Orthodontic traction (with or without coronectomy) provides a gradual, controlled approach intended to minimize direct trauma (6, 7, 9, 22, 31–33). However, its role in clinical practice needs further consideration.

Orthodontic traction is a conservative treatment that is not a risk-free procedure (4, 6, 7, 20, 28, 29). Excessive or inappropriate force could produce root resorption, periodontal injury or movement of the tooth into potentially dangerous anatomical structures and spaces (13–15). Detachment of a bonded attachment or failure of anchorage may delay treatment and require a second surgical exposure (3, 16, 18–21). A recurrent infection or failure to maintain adequate orthodontic hygiene, could influence the surgical site and need prompt attention.

Choosing between extraction and orthodontic traction requires evaluation of anatomy, patient age, and root development. Favourable candidates are typically younger individuals with incomplete root formation, adequate eruption space, and a high predicted risk of nerve injury if surgical removal is performed (1, 8, 9, 17, 28). Unfavourable conditions include ankylosis, excessive root curvature, active infection, or very limited space (20).

Surgical extraction is usually necessary for teeth with infection, cystic change, or unfavourable angulation where movement is unlikely to succeed (1, 7, 9, 17). However, even with modern imaging and modern surgical techniques, the incidence of inferior alveolar nerve injury after high-risk extractions remains clinically significant. Lingual nerve disturbance can also affect quality of life. The advantage of orthodontic traction allows gradual bone remodeling and may reduce acute mechanical stress on the neural tissues. This controlled technique may lead to a lower rate of long-term neurosensory complications, particularly when cone beam computed tomography (CBCT) confirms intimate root and IAN canal contact (6, 9, 16).

Currently, the literature on orthodontic traction of mandibular third molars is limited to small cohort studies and case series. Usually, favourable outcomes are achieved, when treatment is carried out in young patients with incomplete root formation, but these findings cannot be generalized (1, 8, 17). Few studies include long-term neurosensory follow-up, and variations in force magnitude, anchorage systems, and monitoring protocols, which make comparison difficult. There is also a lack of randomized controlled trials that directly compare traction with immediate extraction in defined high-risk groups. Until such data become available, clinicians must base decisions on anatomical risk factors, patient preference, and professional expertise.

Successful third molar traction depends on close professional cooperation between oral surgeons and orthodontists. Oral surgeons provide the surgical exposure and guide the risk assessment. Orthodontists manage the force and the placement of the orthodontic appliance. Treatment duration may be done over several months or longer, depending on the patient's compliance and regular reviews (9, 28, 30). Inadequate follow-up or poor oral hygiene may affect the results or lead to infection.

Furthermore, the movement of the tooth is not always predictable. Ankylosis, unfavourable root morphology, or unexpected migration toward the inferior alveolar canal could change the treatment plan to surgical extraction (1, 7, 9, 17). Coronectomy combined with traction may address some of these challenges but requires careful monitoring for root migration or secondary pathology.

Because both extraction and orthodontic traction carry distinct risks, shared decision-making is central to responsible oral care. Patients should be informed about the risk for nerve injury with either approach, the duration

Tab. 2 A summary of key research findings regarding patient selection, the impact of age on root development, and the necessity of interdisciplinary planning.

Statement	Relevant Citations	Notes on Relevance
Choosing between extraction and orthodontic traction requires evaluation of anatomy, patient age, and root development. Favourable candidates are typically younger individuals with incomplete root formation, adequate eruption space, and a high predicted risk of nerve injury if surgical removal is performed	1, 8, 9, 17, 28	Discusses root development, growth pattern, anatomical considerations, orthodontic traction feasibility, and nerve injury risk.
Orthodontic traction is a conservative treatment that is not a risk-free procedure	9, 28, 20, 29, 30	Covers procedural risks, iatrogenic possibilities, anchorage devices, and technical challenges of traction.
Surgical extraction is the most common treatment approach and has a well documented risk for temporary or permanent sensory disturbance	4, 5, 6, 7, 11, 18, 19, 21, 31–35	Reports incidence, risk factors, preventive strategies, coronectomy comparisons, and clinical outcomes of IAN and LN injury.
Surgical extraction is usually necessary for teeth with infection, cystic change, or unfavourable angulation where movement is unlikely to succeed	1, 7, 9, 17, 28	Addresses anatomical constraints, cystic or pathological changes, and limitations of orthodontic movement.
The advantage of orthodontic traction allows gradual bone remodeling and may reduce acute mechanical stress on the neural tissues. This controlled technique may lead to a lower rate of long-term neurosensory complications, particularly when CBCT confirms intimate root and IAN canal contact	6, 9, 16, 28	Covers gradual orthodontic movement, reduced neural stress, and CBCT-guided planning for nerve safety.
Usually, favourable outcomes are achieved, when treatment is carried out in young patients with incomplete root formation, but these findings cannot be generalized	1, 8, 17	Discusses patient age, root formation, and variability of treatment outcomes.
Treatment duration may be done over several months or longer, depending on the patient's compliance and regular reviews	9, 28–30	Highlights the gradual nature of orthodontic traction, dependence on patient compliance, and anchorage techniques.
Ankylosis, unfavourable root morphology, or unexpected migration toward the inferior alveolar canal could change the treatment plan to surgical extraction	1, 7, 9, 17, 28	Addresses anatomical/morphological constraints, nerve proximity, and limitations of orthodontic traction.
Comparison of nerve injury after surgical extraction and coronectomy shows IAN injury in 0.35%–1.5% and LN injury in 0.1%–1.8%	5, 18, 19, 31–35	Reports incidence of nerve injury in extraction and coronectomy; comparative studies included.
Permanent deficits were generally lower, with IAN involved in 0.33%–0.6% and LN in 0.1%–1.1%	5, 18, 31–35	Focuses on permanent nerve injury incidence after extraction and coronectomy.
Overall, coronectomy appears to reduce the immediate risk of nerve injury compared with complete surgical extraction, particularly for teeth in proximity to the IAN. Long-term monitoring is needed because retained roots can migrate or occasionally require secondary intervention	7, 31–35	Covers nerve benefits, retained root behaviour, migration, and need for follow-up.

Tab. 3 Statistical overview of temporary and permanent sensory deficits associated with the inferior alveolar nerve (IAN) and lingual nerve (LN) across different surgical techniques.

Procedure	IAN Injury (Temporary)	LN Injury (Temporary)	IAN Injury (Permanent)	LN Injury (Permanent)	Notes
Surgical Extraction	0.35%–1.5%	0.1%–1.8%	0.33%–0.6%	0.1%–1.1%	Most common treatment. Risk influenced by root proximity, angulation, and patient anatomy (5, 18, 19).
Coronectomy	~0.1%–0.6%	~0.1%–1.2%	0.1%–0.6%	0.1%–1.1%	Reduces immediate IAN injury risk. Retained roots may migrate and require long-term monitoring (7, 31–35).

of orthodontic treatment, and the possibility of surgical removal even after months of traction. A clear explanation of these factors supports informed consent and sets realistic expectations.

According to the reviewed studies, a comparison of nerve injury after surgical extraction and coronectomy of mandibular third molars can be concluded that inferior alveolar nerve (IAN) injury occurred in 0.35% to 1.5% of cases, while lingual nerve (LN) injury ranged from 0.1% to 1.8%. Permanent deficits were generally lower, with IAN involved in 0.33%–0.6% and LN in 0.1%–1.1%. Additionally, in systematic reviews and clinical studies, IAN injury after successful coronectomy was lower, around 0.5%–1.3%, and LN injury was very rare, approximately 0.05%. Failed coronectomies had higher IAN injury (up to 2.6%), but permanent paraesthesia remained uncommon (0.05%–1.3%) (5, 18, 19, 31–35).

Overall, coronectomy appears to reduce the immediate risk of nerve injury compared with complete surgical extraction, particularly for teeth in proximity to the inferior alveolar nerve (7, 33). Long-term monitoring is needed because retained roots can migrate or occasionally require secondary intervention (32, 34). Table 2 summarizes the key studies supporting important statements, detailing relevant research on orthodontic traction, surgical extraction, coronectomy, and associated nerve injury by highlighting patient age, root development, anatomical considerations, treatment duration, and complication rates. The comparative data indicate that surgical extraction of mandibular third molars carries a higher immediate risk of inferior alveolar and lingual nerve injury, whereas coronectomy appears to reduce this risk, particularly for teeth in close proximity to the nerve, although long-term monitoring is required due to potential root migration and delayed complications (Table 3).

Advances in imaging, such as high-resolution CBCT and three-dimensional modelling, may define selection criteria and improve the prediction of root movement relative to the mandibular canal. Development of standardized force protocols and anchorage systems would allow for a more meaningful comparison of outcomes. Prospective multi-centre trials with long-term evaluation are needed to specify the true benefit of orthodontic traction in preventing neurosensory injury.

Several gaps in the current research on nerve injuries on coronectomy versus surgical extraction can be identified. Also, comparative studies directly evaluating cost-effectiveness and procedure time between coronectomy and full extraction are limited.

Future research could focus on large, multicentre, prospective trials with standardised definitions of nerve injury and uniform follow-up intervals. Longitudinal studies examining root migration and the need for secondary interventions would clarify long-term safety. Inclusion of patient-reported outcomes and economic analyses could provide a more comprehensive assessment of the clinical and social impact. Finally, studies exploring predictive imaging markers or risk stratification tools may help identify patients who would benefit most from coronectomy versus surgical extraction.

CONCLUSION

Orthodontic traction with coronectomy or without provides a conservative option for carefully chosen patients in whom surgical extraction carries an identified risk of nerve injury. While preliminary evidence suggests a lower incidence of temporary and permanent nerve injury, the method requires sustained collaboration, precise biomechanical control, and a willingness to accept longer treatment times. Until stronger data are available, the decision between orthodontic traction and surgical extraction should remain individualized, guided by detailed imaging, patient factors, and the clinician's experience.

Long-term follow-up in coronectomized teeth regarding retained root migration, late complications, and secondary interventions is limited. Additionally, patient-reported outcomes, such as sensory recovery, functional impact, and quality of life, are not consistently evaluated, making it difficult to fully assess the clinical implications of each technique.

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Comparison between the Prognosis of Temporomandibular Disorders with and without Accompanying Otologic Symptoms after Non-Invasive Non-Pharmacological Treatment: Controlled Clinical Trial

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ABSTRACT

Background: Otologic symptoms are commonly reported by patients with temporomandibular disorders.
Objective: This study aims to investigate the likely outcome or progression of temporomandibular disorders with and without accompanying otologic symptoms when treated in the dental clinic.
Methods: The study is registered under the International Standard Randomised Controlled Trial Number: ISRCTN49976724, DOI: 10.1186/ISRCTN49976724. Forty patients with temporomandibular disorders were included and allocated into two groups: Control group (n=20): isolated temporomandibular disorders symptoms, and Experimental group (n=20): temporomandibular disorders symptoms with otologic symptoms (confirmed by otorhinolaryngological evaluation to exclude primary ear pathology). All participants underwent non-invasive, non-pharmacological treatment. The treatment contained physiotherapy and custom-made occlusal splints. Outcomes (full/partial/no recovery) were assessed at 3 months by a single maxillofacial surgeon, with follow-up every 3 weeks. Statistical analysis included Fisher's exact test and odds ratios.
Results: Fisher's exact test revealed a statistically significant association between group allocation and recovery outcomes (χ^2=5.979, p=0.041). The odds ratio was 5.33.
Conclusion: The presence of otological symptoms accompanying temporomandibular disorders might predict a better prognosis after non-invasive, non-pharmacological treatment, perhaps not as a direct predictor per se but as a confounding factor.

KEYWORDS

temporomandibular joint disorders; occlusal splints; treatment outcome; prognosis; otolaryngology; physical therapy modalities

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INTRODUCTION

Temporomandibular disorders (TMD) are a group of multifactorial conditions affecting the temporomandibular joint (TMJ), muscles of mastication, and related structures. Epidemiological studies reported a high prevalence ranging between 40% and 60% (1).

Otologic symptoms are commonly reported by patients with TMD, with an 87% comorbidity rate (2). A 2017 systematic review and meta-analysis quantified the prevalence of otologic symptoms associated with TMD, revealing: ear fullness 74%, otalgia 55%, tinnitus 52%, vertigo 40%, and hearing loss 38% (3).

Different theories about the pathophysiology correlating the otologic symptoms to TMD originate from both anatomical and neurological mechanisms. Anatomically, the auditory tube (4) and the discomalleolar ligament (5) create direct structural continuity between the TMJ and the middle ear. The discomalleolar ligament was described by Pinto in 1962, but because it was historically grouped with the anterior malleolar ligament or labelled as retrodiscal tissue, older classical anatomy textbooks often lack a specific description of this important anatomical structure, which connects the malleus in the tympanic cavity and the articular disc and capsule of the temporomandibular joint (6, 7). Furthermore, the TMJ and ear share some embryonic and anatomic-topographic origins, which can lead to secondary otologic symptoms when the TMJ is affected (8). Neurologically, both central sensitization (9) and neurophysiological convergence through the trigeminal nerve innervation (10) may contribute to the involvement of the central and peripheral nervous systems, respectively (11).

Early diagnosis and management of TMD are likely to improve prognosis and reduce healthcare costs for patients (12). Conservative treatments like occlusal splints and physiotherapy are effective first-line interventions for many patients (13).

Existing studies have identified multiple predictors of TMD including: arthralgia (14), cervical musculoskeletal dysfunction (15), parafunctional habits like bruxism (16), greater baseline pain intensity (17), and psychological distress (particularly anxiety and depression) (18). However, otologic symptoms remain absent from prognostic models despite their high prevalence and clinical significance. This is mainly because they are not included in most standardized diagnostic tools like the DC/TMD Diagnostic Criteria for Temporomandibular Disorders (19).

This represents a critical knowledge gap, as otologic symptoms may represent either a secondary phenomenon resulting from anatomical proximity and shared innervation or markers of a distinct TMD subtype with different treatment responsiveness. Current prognostic models cannot account for this possible variability, potentially leading to suboptimal treatment stratification.

To our knowledge, no previous studies have investigated the correlation between TMD and accompanying otologic symptoms using a prognosis-oriented approach (20, 21) rather than a diagnosis-oriented one.

This study is addressing this gap by investigating whether the otological symptoms accompanying TMD can be considered as a predictor. The null hypothesis of this research work stated that there was no relationship between the prognosis of TMD and the presence of accompanying otologic symptoms.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANT ALLOCATION

This study was a single-centre interventional controlled clinical trial. It was approved by the Research Ethical Committee at Al-Sham Private University on 09.09.2024 with ID number: REC002 in accordance with the Helsinki Declaration. The study was registered with ISRCTN Registry under reference ISRCTN49976724, DOI: https://doi.org/10.1186/ISRCTN49976724.

PATIENT RECRUITMENT

Participants entered the study through three routes: 1-Self-referred patients: individuals presenting directly to the TMD clinic. 2-General dentist referrals: patients referred by general dental practitioners for suspected TMD. 3-Otorhinolaryngological referrals: patients redirected to the clinic by otolaryngologists after the exclusion of primary ear-related pathology. A total number of 40 patients with temporomandibular disorders (TMD) were enrolled. They were divided into two groups: the control group (n=20), comprising patients with only TMD symptoms, and the experimental group (n=20), comprising patients with TMD accompanied by otologic symptoms. Written informed consent was obtained from all patients.

The control group comprised first 20 consecutive self-referred or dentist-referred patients with only TMD symptoms (no otologic symptoms), requiring no otorhinolaryngological evaluation. On the other hand, the experimental group comprised patients from all three pathways who reported otologic symptoms. For self-referred and dentist-referred patients in this group, otorhinolaryngological confirmation was mandatory to exclude primary ear-related pathology. Only the first 20 patients who met this criterion were enrolled.

A single maxillofacial surgeon conducted all study parts: clinical examination, diagnosis, eligibility assessment, non-invasive, non-pharmacological treatment, and follow-up evaluations. This ensures consistency in data collection and intervention delivery.

The diagnostic process began with a comprehensive review of each patient's medical and dental history, emphasizing TMD and otological symptoms. A systematic manual examination of the TMJ was then conducted in accordance with the standardized methodology described by Bumann and Lotzmann (22). This involved palpation of masticatory muscles for tenderness, auscultation for joint sounds during mandibular movements, and functional assessment of maximal interincisal opening, lateral excursions, and protrusive range.

Radiographic evaluation was reserved for cases requiring diagnostic clarification. Initial screening utilized panoramic radiography (orthopantomogram) to identify gross bony abnormalities, such as fractures or degenerative changes. When clinically warranted, tomographic

imaging in open and closed mouth positions provided cross-sectional views to detect subtler pathologies, including erosions, osteophytes, or intra-articular adhesions. Magnetic resonance imaging (MRI) was selectively employed to evaluate soft tissue structures like articular disc position.

Definitive diagnoses were established by synthesizing clinical findings, imaging results (where applicable. All evaluations, including diagnosis and subsequent treatment planning, were conducted by a single maxillofacial surgeon to ensure methodological consistency. The treatment approach was identical for both groups and tailored to individual clinical presentations.

PHYSIOTHERAPY AND OCCLUSAL SPLINT THERAPY

Physiotherapy: Both groups underwent identical non-invasive, non-pharmacological therapy combining physiotherapy and occlusal splint therapy. Physiotherapy aimed to reduce musculoskeletal tension and improve joint function through these techniques: massage, moist heat pack application, and infrared thermotherapy. Moreover, patients identified with joint compression during diagnosis were instructed to perform stretching exercises. Massage, moist heat pack application, and infrared thermotherapy were applied during clinical appointments every three weeks, while the stretching exercises were self-administered every day.

The massage was performed bilaterally to all the patients and lasted approximately twenty minutes per session. It targeted the primary masticatory and temporal muscles, specifically the anterior bundle of the temporalis and the upper fibres of the masseter, with additional attention to the suprahyoid musculature. The massage session began with three minutes of gentle surface sliding over the anterior temporalis in a counter-clockwise circular motion, followed by three minutes of cranial-to-caudal kneading of the upper masseter fibres. During kneading, the hands returned to the initial position with continuous caudal-to-cranial sliding along the suprahyoid musculature. This sequence of alternating surface sliding over the temporalis and kneading of the masseter was repeated in shorter durations (1 minute each) two more times to maintain tissue engagement and prepare for deeper work. Subsequently, deeper sliding over the temporalis was performed for three minutes, followed by three minutes of deeper kneading of the masseter, maintaining the cranial-caudal direction and suprahyoid return. This sequence of alternating deep sliding over the temporalis and deep kneading of the masseter was repeated in shorter durations (1 minute each), two more times, culminating in a brief light-touch at the end of the session. Throughout, circular movements over the temporalis and cranial-caudal kneading of the masseter were performed in a controlled, systematic manner to ensure effective stimulation of the targeted musculature. This massage technique was adapted from the approach described by El Hage et al. (2013) (23).

Moist heat packs (40–42 °C) were applied bilaterally to the masseter and temporalis muscles to all the patients in a supine position for 10 minutes per session. The temperature was maintained using hydrocollator packs (Chattanooga Group, Tennessee, USA) wrapped in a terrycloth towel to prevent thermal injury. The duration and technique of applying moist heat packs were adapted from a pilot study by Azam et al. (2023) (24).

The infrared thermotherapy was administered bilaterally to all the patients to alleviate muscle stiffness and relieve pain. The total session duration was 20 minutes, with 10 minutes for each side. The session started with positioning the patient in a well-supported posture, and the nature and effects of the treatment were explained to the patient. An infrared radiator (Philips PAR38 Healthcare IR 150W 230V, Amsterdam, Netherlands) was positioned 40 centimetres from the skin surface and maintained to target both the masseter and temporalis muscles at or near right angles to achieve maximum penetration. Adjacent areas, including the eyes, were protected from heating by the placement of a layer of towelling. Throughout each session, the clinician monitored for cutaneous erythema as a safety measure, prepared to discontinue treatment immediately if any adverse reactions occurred. The thermotherapy was conducted in accordance with the guidelines described in Electrotherapy: Principles and Practice (25).

Stretching exercises were administered by the clinician to the affected joint, consisting of three 5-minute repetitions (totalling 15 minutes for unilateral involvement or 30 minutes for bilateral cases). The technique, described by Bumann and Lotzmann, required the patient to open the mouth to the first level of muscle tension and then exert a light isometric force against the clinician's thumb. This technique causes the contractile muscle cells to stretch the noncontractile elements (22).

All patients were instructed to adhere to a soft diet to minimize mechanical strain on the TMJ.

Custom occlusal splints were fabricated using conventional dental techniques (26). Initial diagnostic impressions of the maxillary and mandibular arches were obtained with alginate (Hydrogum, Zhermack SpA, Badia Polesine, Italy) material to replicate dental anatomy, followed by a wax bite registration with a hard baseplate wax (Beauty Pink Wax, Moyco, York, USA) to establish an optimized mandibular position. Three types of occlusal splints were utilized according to the specific TMD conditions: relaxation splints, decompressing splints, and anterior repositioning splints. These splints are used to stabilize occlusion, to compensate for loss of vertical dimension, and to guide the mandible into a protrusive position, respectively (27). All occlusal splints were designed and fabricated based on individual clinical findings and the severity of the case.

OUTCOME MEASURES

Patients attended follow-up evaluations at three-week intervals to monitor therapeutic progress and optimize treatment adherence. During these visits, the maxillofacial surgeon assessed symptom progression, adjusted occlusal splints to maintain proper fit and functional alignment individually with consideration of the splint type,

Tab. 1 Baseline sample characteristics.

Characteristic	Control group (n=20)	Experimental group (n=20)	Total (N=40)
Mean age, years	25.5	31.5	28.5
Standard deviation, years	10.62	13.07	12.14
Median age, years	21.5	27.5	25
Gender, n (%)	Male: 2 (10%)	Male: 7 (35%)	Male: 9 (22.5%)
	Female: 18 (90%)	Female: 13 (65%)	Female: 31 (77.5%)

and reinforced physiotherapy techniques as needed. Clinical feedback from patients, including subjective reports of pain reduction or functional improvement, guided iterative refinements to the therapeutic regimen. The endpoint for outcome assessment was defined at three months post-intervention, regardless of whether the treatment was finished for each individual patient or not.

Outcomes of the TMD symptoms were categorized as full recovery (complete resolution of TMD and otologic symptoms, if present), partial recovery (defined as any reduction in symptom severity), or no recovery (no improvement or worsening symptoms). TMD symptoms severity was evaluated using standardized clinical criteria, including the visual analogue scale (VAS) for pain intensity, mandibular mobility measurements, and the frequency of joint crepitus. Mandibular mobility was measured for opening, lateral excursion, and protrusive movements.

STATISTICAL ANALYSIS

The SAS Studio software, release: 3.82 enterprise edition (SAS Institute Inc., Cary, North Carolina, USA) was used to perform statistical analyses. Fisher's exact test was used to examine the association between group allocation and recovery outcomes. In order to examine if there was a relationship between age and recovery status, the non-parametric test, Kruskal-Wallis, was used.

RESULTS

BASELINE SAMPLE CHARACTERISTICS

Baseline characteristics of the participants are summarized in Table 1. The mean age of the Control group was 25.5 ±10.62 years, the median age was 21.5 years, and 10% were male. Whereas the mean age of the Experimental group was 31.5 ±13.07 years, the median age was 27.5 years, and 35% were male.

RECOVERY OUTCOMES

At the 3-month endpoint, 32.5% (n=13) of participants achieved full recovery, 65% (n=26) showed partial recovery, and 2.5% (n=1) reported no improvement.

The experimental group demonstrated a significantly higher rate of full recovery (50%, n=10) compared to the control group (15%, n=3). Conversely, partial recovery predominated in the control group (80%, n=16), while the experimental group split evenly between full and partial recovery (50% each, n=10). No participants in the experimental group exhibited "no recovery," whereas one case (5%) persisted in the control group (Table 2).

Fisher's exact test revealed a statistically significant association between group allocation and recovery outcomes (χ^2=5.979, p=0.041), indicating that recovery patterns differed meaningfully between the control and experimental groups. To quantify this effect, an odds ratio was calculated for full versus partial recovery (excluding the single "no recovery" case). Participants in the experimental group had 5.33 times higher odds of achieving full recovery compared to the control group (odds in control: 0.1875; odds in experimental: 1; OR=5.33).

The Kruskal-Wallis test showed no significant difference in the age of patients across the recovery pattern groups (p=0.968).

DISCUSSION

This study observed a significantly higher prevalence of TMD in females than in males, which aligns with other epidemiological studies (28–30). Females are more susceptible to developing TMD due to hormonal (31, 32), behavioural (33), and psychological (34) factors.

A recent study that established a clinical profile of patients with TMD in relation to age and gender found that TMD is most frequently reported in young to middle-aged adults, with a peak incidence between 20 and 40 years,

Tab. 2 Cross-tabulation of recovery outcomes by group.

Outcome	Type	Group		
		Control group	Experimental group	Total
Recovery	Full Recovery	3 (7.5%)	10 (25%)	13 (32.5%)
	Partial Recovery	16 (40.2%)	10 (25%)	26 (65%)
	No Recovery	1 (2.5%)	0 (0%)	1 (2.5%)
	Total	20 (50%)	20 (50%)	40 (100%)

affecting females more than males (35). These findings are consistent with the results of the present study.

This present study demonstrated a statistically significant association between TMD symptom profiles (with or without otologic symptoms) and treatment outcomes following non-invasive therapy. Thus, rejecting the null hypothesis. The experimental group (TMD + otologic symptoms) exhibited 5.33 times higher odds of full recovery compared to the control group (TMD only), with no cases of "no recovery" in the former. This suggests that otologic symptoms in TMD patients may not necessarily indicate poorer prognosis, contrary to some clinical assumptions, but could instead reflect a subtype more responsive to non-invasive, non-pharmacological therapies like occlusal splints and physiotherapy.

The observed disparity in recovery rates (50% full recovery in the experimental group vs. 15% in controls) raises questions about potential mechanistic differences.

Studies indicate that otological symptoms like earache and tinnitus can appear early in the progression of TMD. For instance, otological symptoms in TMD may stem from referred muscular tension (36) or Eustachian tube dysfunction (37), both of which could be alleviated by splint-induced joint repositioning or muscle relaxation, as two systematic reviews show (38, 39).

Naderi et al. found that non-invasive, non-pharmacological TMD treatments relieved both TMD and associated otological symptoms. The splints are significantly efficient in improving otologic symptoms, with more than 50% of the patients reporting complete or partial recovery after a 2-month follow-up (40).

Conversely, isolated TMD symptoms might involve more entrenched articular or degenerative pathology, requiring more extended intervention periods. This is supported by findings that show a significant association between TMD severity and treatment duration (41). There is a significant association not only between otologic symptoms and jaw functions (such as speaking, opening, and closing the mouth) but also between the severity of otologic symptoms and the severity of other TMD symptoms (42). A potential confounding factor in this association is that patients experiencing difficulties with jaw functions are more likely to seek medical care earlier in the course of TMD (43), whereas those with painless TMJ clicking may ignore their symptoms (44). This difference in care-seeking behaviour could influence the observed relationship between the prognosis of TMD symptoms and the presence of the accompanying otologic symptoms after non-invasive, non-pharmacological treatment.

Since the group assignment is predetermined by an external factor, which is the presence or absence of otological symptoms, this study design exhibits robust external validity (45). Nevertheless, it is accompanied by an inherent limitation of internal validity (46).

Another limitation of this study is the 3-month endpoint, which only shows short-term improvements. While patients requiring extended care received additional follow-up for up to six months, data beyond the three-month endpoint were excluded from formal analysis to provide consistency within the group. This would guarantee that comparisons of outcomes between groups would be based on an identical timeframe, preventing confounding due to different treatment durations.

Further investigation is needed to explain the mechanism of how the otological symptoms are affecting the prognosis and to assess long-term improvements.

CONCLUSIONS

Within the limitations of this study, it can be concluded that otologic symptoms may paradoxically predict better TMD recovery. In other words, the presence of otological symptoms accompanying TMD might predict a better prognosis after non-invasive, non-pharmacological treatment, perhaps not as a direct predictor per se but as a confounding factor.

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Growth Hormone-Mediated Diabetic Ketoacidosis: A Rare Presentation of Acromegaly

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ABSTRACT

Acromegaly is a chronic disorder caused by pathological hypersecretion of growth hormone (GH), most commonly due to pituitary somatotroph adenomas. Excess GH leads to elevated insulin-like growth factor 1 (IGF-1) levels, which together mediate progressive physical changes and a wide range of systemic complications. A key metabolic abnormality in acromegaly is impaired glucose metabolism, which may result in diabetes through mechanisms of insulin resistance. This report describes a case of diabetic ketoacidosis (DKA), a severe complication of relative insulin deficiency, presenting as a rare initial manifestation of acromegaly. Following surgical intervention and remission of acromegaly, the glycemic control of the patient significantly improved, underscoring the importance of addressing the underlying endocrinopathy. This report highlights the critical need for comprehensive clinical evaluations in patients with common metabolic disorders, such as diabetes mellitus, to identify rare underlying causes and ensure timely diagnosis. Furthermore, it examines potential mechanisms of ketosis in acromegaly and reviews current approaches to glycemic management in this population, where evidence-based guidelines remain limited.

KEYWORDS

diabetic ketoacidosis; acromegaly; pituitary adenoma; hyperprolactinemia

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INTRODUCTION

Acromegaly is an endocrine disorder characterized by chronic hypersecretion of growth hormone (GH), most commonly resulting from a pituitary somatotroph adenoma. Excess GH and its downstream effector, insulin-like growth factor-1 (IGF-1), result in characteristic phenotypic changes and a broad spectrum of systemic complications, including cardiovascular, respiratory, metabolic, musculoskeletal, and neurological involvement (1, 2). In addition, tumor mass effects may cause headaches or visual disturbances.

A major metabolic consequence of acromegaly is impaired glucose homeostasis, with diabetes mellitus reported in up to 53% of affected patients (3, 4). Furthermore, the prevalence of acromegaly among individuals with diabetes is 25- to 75-fold higher than in the general population (3, 5). The presence of diabetes in acromegaly is associated with diminished quality of life and adverse long-term prognosis. While insulin resistance is the principal mechanism underlying metabolic complications in acromegaly (6), this report describes a case of diabetic ketoacidosis (DKA), indicative of an absolute or relative insulin deficiency state, as the initial clinical manifestation of acromegaly. This study also discusses the underlying pathophysiology and therapeutic strategies for managing diabetes in this context.

CASE REPORT

A 46-year-old woman presented with a 5-day history of epigastric pain and dyspnea. Her medical history was notable for unintentional weight loss of 6 kg over the preceding 4 months. On admission, she was febrile (37.8 °C), tachycardic (120 beats/min), and exhibited Kussmaul respirations, with a blood pressure of 136/90 mmHg and a body mass index (BMI) of 28.48 kg/m² (weight 72 kg). Initial laboratory studies showed severe hyperglycemia, a plasma glucose level of 503 mg/dL and an HbA1c of 12.3%. Serum b-hydroxybutyrate was elevated at 3.9 mmol/L (reference 0.2–0.27 mmol/L; enzymatic spectrophotometric assay). Mild azotemia was present, with blood urea nitrogen of 50 mg/dL (reference 7–20 mg/dL) and serum creatinine of 1.9 mg/dL (reference 0.6–1.1 mg/dL). Serum electrolytes showed sodium 133 mmol/L, potassium 3.8 mmol/L, chloride 105 mmol/L, and bicarbonate 11 mmol/L, with an anion gap of 17 mmol/L. Venous blood gas analysis indicated metabolic acidosis with pH 7.254, pCO_2 15.1 mmHg, and HCO_3 6.7 mmol/L. Serum lactate was normal at 0.9 mmol/L

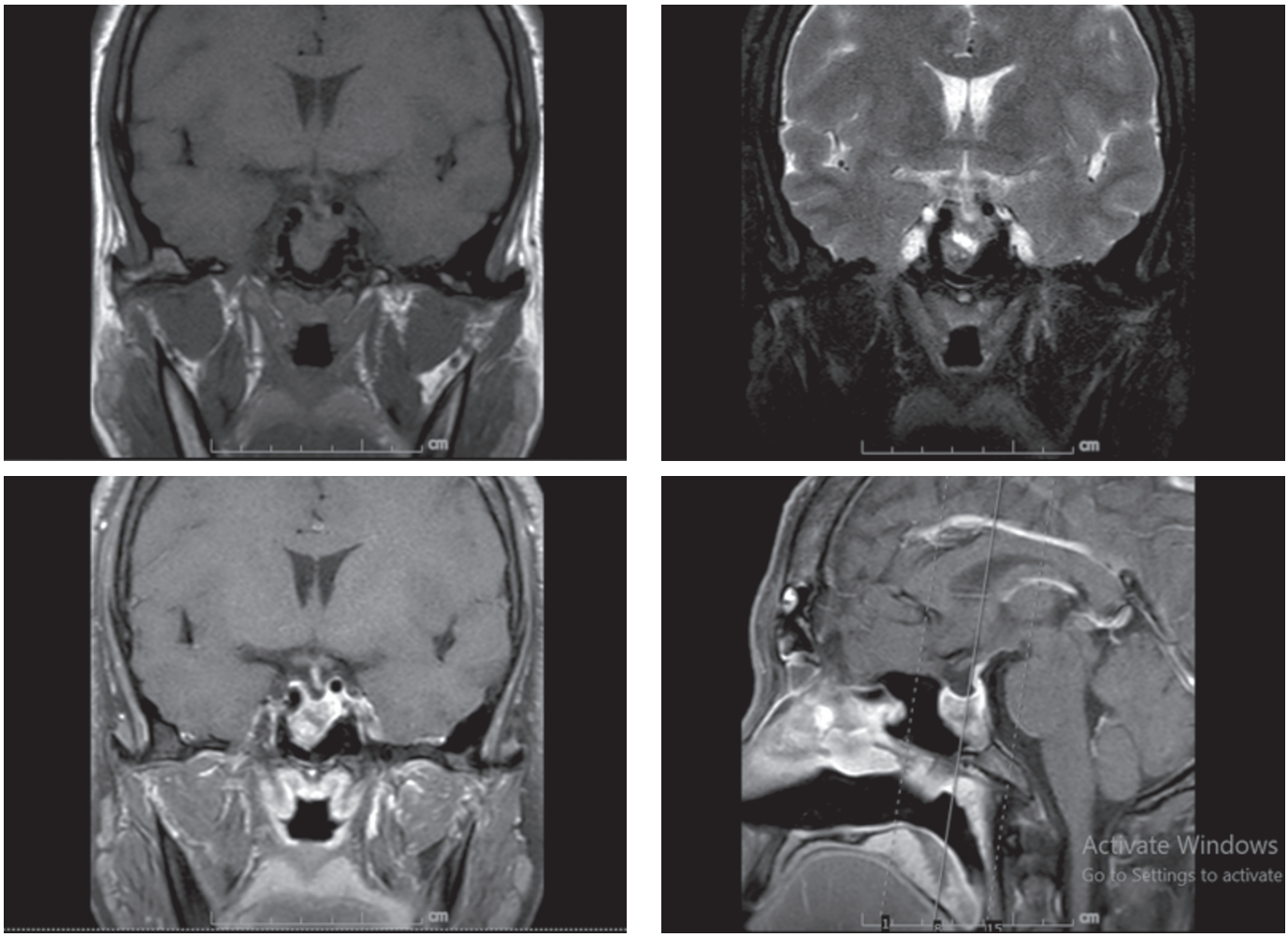

Fig. 1 Pituitary MRI showing a heterogeneously enhancing intrasellar mass (1.7×1.9×1.9 cm) with inferior extension into the sphenoid sinus. Coronal views: (A) T1-weighted, (B) post-contrast T1-weighted, (C) T2-weighted; (D) sagittal view.

(reference 0.5–2.0 mmol/L) and the effective serum osmolarity was 293 mOsm/kg (reference 275–295 mOsm/kg). Complete blood count revealed leukocytosis (white blood cell count, 12.0×10⁹/L) with marked neutrophilia (92%). The patient was diagnosed with DKA precipitated by primary *Klebsiella pneumoniae* bacteremia without an identifiable source of infection. Management was initiated according to institutional DKA protocols, including aggressive intravenous fluid resuscitation with isotonic saline, continuous intravenous insulin infusion at 7 units/hour, potassium supplementation, and close biochemical monitoring. Ketoacidosis resolved within 12 hours, after which insulin therapy was transitioned to a subcutaneous basal-bolus regimen, with subsequent normalization of renal function and serum electrolytes. Intravenous ceftriaxone was started based on antimicrobial susceptibility testing and subsequently de-escalated to oral amoxicillin-clavulanate on hospital day 7 to complete a 14-day course. The patient was discharged in stable condition on subcutaneous premixed insulin, with a total daily dose of 90 units.

Further history revealed progressive facial changes, a 10-kg weight gain, increased snoring, and amenorrhea over the past 6 years. Re-examination revealed distinctive acromegalic features, including frontal bossing, macroglossia, prognathism, and spade-like hands. Ophthalmologic evaluation demonstrated normal visual fields and fundoscopic findings. Hormonal evaluation confirmed the diagnosis of acromegaly, with markedly elevated IGF-1 levels at 662 ng/mL (reference 74–196 ng/mL) and non-suppressible GH during an oral glucose tolerance test (OGTT) (nadir GH 22.8 ng/mL; normal <1 ng/mL). Prolactin was moderately elevated at 100.3 ng/mL (reference 5.2–26.5 ng/mL). Thyroid function tests showed euthyroid state: thyroid-stimulating hormone (TSH) 1.028 mIU/mL (reference 0.70–1.48 mIU/mL), free thyroxine (FT_4) 0.99 ng/mL (reference 0.35–4.94 ng/mL). Morning cortisol was within normal ranges at 7.0 mg/dL (reference 3.7–19.4. mg/dL). Gonadotropin levels were follicle-stimulating hormone (FSH) 11.0 mIU/mL (reference 3.03–8.08 mIU/mL), luteinizing hormone (LH) 3.1 mIU/mL (reference 1.8–11.78 mIU/mL), and estradiol < 5.00 pg/mL (follicular-phase reference 21–251 pg/mL), consistent with hypogonadism. Pituitary magnetic resonance imaging (MRI) identified a macroadenoma without optic chiasm compression (Figure 1). The patient underwent transsphenoidal surgery with complete tumor resection, and histopathological examination confirmed a mammosomatotroph adenoma (Figure 2). At the 6-month follow-up, biochemical remission was achieved, with normalized IGF-1 levels (160.2 ng/mL), appropriate GH suppression, and normal prolactin levels. Follow-up MRI demonstrated

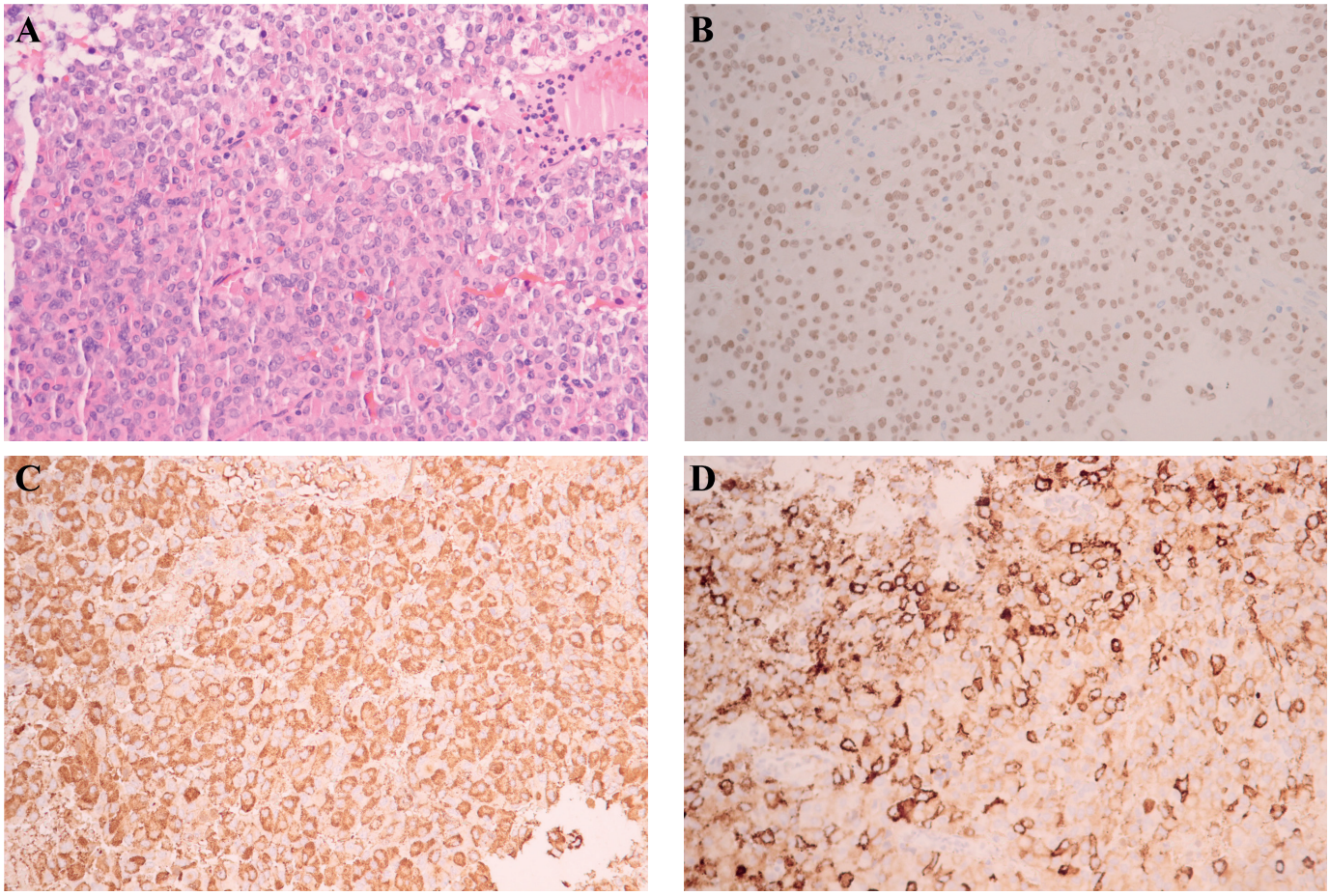

Fig. 2 Histology of the pituitary tumor. (A) H&E stain (40×) showing tumor cells with round nuclei, distinct nucleoli, stippled chromatin, and eosinophilic cytoplasm. Immunohistochemistry showing positive staining for (B) nuclear PIT-1, (C) cytoplasmic GH, and (D) cytoplasmic prolactin.

no residual tumor. Glycemic control improved significantly, with HbA1c decreasing to 6.5%, allowing discontinuation of insulin therapy. Subsequent evaluation revealed preserved b-cell function (C-peptide 3.0 ng/mL; reference 0.78–5.19 ng/mL) and negative anti-glutamic acid decarboxylase (anti-GAD) antibodies. Optimal glycemic control was maintained with combined dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin therapy.

DISCUSSION

Acromegaly presents a significant diagnostic challenge due to its insidious clinical progression and frequent misdiagnosis as more common conditions. Consequently, diagnosis is often delayed by five to ten years (7), which increases the risk of preventable complications such as cardiovascular diseases, metabolic derangements, and malignancies (1, 8). This case report illustrates that GH excess can precipitate severe dysglycemic states, notably DKA, and also highlights the diagnostic and therapeutic challenges of managing diabetes secondary to acromegaly.

The metabolic actions of GH and IGF-1 mediate the disordered carbohydrate metabolism observed in acromegaly. GH exerts predominantly diabetogenic effects by inducing hepatic and peripheral insulin resistance, which results in reduced glucose uptake and increased hepatic gluconeogenesis. In contrast, IGF-1 enhances insulin sensitivity and stimulates pancreatic b-cell insulin secretion; however, these compensatory mechanisms are insufficient to overcome GH-induced insulin resistance, resulting in net hyperglycemia (2, 3, 6). Notably, the characteristics of insulin resistance in acromegaly differ from those observed in type 2 diabetes, as it is primarily mediated by GH excess rather than obesity or visceral adiposity. The severity of these metabolic complications correlates with circulating GH levels and is further influenced by factors such as age, disease duration, BMI, hypertension, female sex, and family history of diabetes (4, 5, 8).

DKA is a life-threatening acute metabolic complication of diabetes mellitus, characterized by hyperglycemia, ketosis, and high-anion gap metabolic acidosis. It results from absolute or relative insulin deficiency, typically in the setting of an elevated glucagon-to-insulin ratio. In acromegaly, chronic GH excess promotes lipolysis, resulting in elevated circulating free fatty acids that enhance hepatic ketogenesis and contribute to b-cell dysfunction through glucolipotoxicity. Consequently, in addition to its effects on insulin resistance, prolonged GH exposure may induce a state of relative insulin deficiency (9, 10). In this patient, longstanding hyperglycemia, reflected by a markedly elevated HbA1c, was likely driven by undiagnosed acromegaly and precipitated into DKA by infection and dehydration. The absence of autoimmune markers and the recovery of endogenous insulin secretion following remission of acromegaly support the reversibility of this metabolically decompensated state. These findings highlight that acromegaly-associated diabetes may progress from isolated insulin resistance to compromised b-cell functional reserve, predisposing susceptible individuals to DKA during metabolic stress, consistent with a ketosis-prone phenotype (11). However, C-peptide, insulin, and glucagon levels were not measured during the acute episode, precluding confirmation of this proposed mechanism.

Diagnosing acromegaly in patients with diabetes presents additional challenges because poorly controlled hyperglycemia may suppress IGF-1 levels and compromise the reliability of the OGTT. Therefore, achieving glycemic control before the hormonal evaluation is essential for accurate interpretation (12, 13). Currently, disease-specific guidelines for managing diabetes secondary to acromegaly remain limited; thus, treatment generally follows standard protocols for type 2 diabetes mellitus (14). Metformin remains the first-line therapy due to its insulin-sensitizing effects and suppression of hepatic glucose production. Incretin-based therapies, including DPP-4 inhibitors and glucagon-like peptide-1 receptor (GLP-1R) agonists, as well as sodium-glucose cotransporter-2 (SGLT2) inhibitors, may be preferred over thiazolidinediones or insulin secretagogues (sulfonylureas and repaglinide) because of their cardiovascular benefits, which are particularly relevant for acromegaly patients at increased cardiovascular risk.

Surgical resection of the adenoma, the definitive treatment for acromegaly, significantly improves glucose tolerance, with diabetes resolving in approximately two-thirds of patients who achieve remission (6, 10). For those with persistent disease or requiring preoperative management, medical options including somatostatin receptor ligands (SRLs), dopamine agonists, and GH receptor antagonists are effective in controlling acromegaly and improving glycemic control. However, pasireotide, a second-generation multi-ligand SRL, may worsen glucose metabolism by suppressing insulin and incretin secretion; therefore, it should be avoided in patients with impaired glucose tolerance or poorly controlled diabetes (15). Radiotherapy, considered a third-line treatment for acromegaly, has inconclusive effects on glucose metabolism.

In our patient, the pathological examination revealed a mammosomatotroph adenoma, a Pit-1 lineage tumor subtype that secretes both GH and prolactin (16). Clinically, this subtype closely resembles a densely granulated somatotroph tumor but is distinguished by more pronounced hyperprolactinemia and a higher prevalence among younger patients with acromegaly or gigantism. While data regarding medical treatment responses are limited, mammosomatotroph adenomas generally respond to somatostatin analogs and may also benefit from dopamine agonist therapy.

CONCLUSION

This case demonstrates DKA as a rare but preventable manifestation of acromegaly. It underscores the importance of comprehensive evaluation in patients with common disorders such as diabetes, which requires thorough history taking, careful physical examination, and appropriate investigations to identify underlying etiologies.

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Transient Occlusion of the Central Retinal Artery in a Patient with Granulomatosis with Polyangiitis

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ABSTRACT

The purpose of this report is to document the occurrence of transient central retinal artery occlusion (CRAO) as a rare and serious ocular complication in a patient with granulomatosis with polyangiitis (GPA), emphasizing the potential vision-threatening nature of this condition. A 49-year-old male with a known diagnosis of GPA presented with transient CRAO. The case was analyzed to understand the ocular manifestations associated with GPA and the challenges in its management. The patient exhibited a transient CRAO, highlighting the potential for severe ocular complications in the context of GPA. Transient CRAO is a rare but serious vision-threatening complication of GPA. This case underscores the importance of early diagnosis and timely management in patients with ocular manifestations of GPA. Financial disclosure: No financial support was received for this case report. None of the authors has any proprietary interests or conflicts of interest related to this submission. It is not simultaneously being considered for publication at any other journal.

KEYWORDS

central retinal artery; granulomatosis with polyangiitis; transient occlusion

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INTRODUCTION

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a form of vasculitis characterized by granulomatous inflammation, necrosis, and vasculitis primarily affecting small- to medium-sized vessels (1). It typically involves the respiratory tract and kidneys but can affect other organs including the eyes (2). Ocular involvement occurs in approximately 30–50% of patients with GPA, most commonly manifesting as scleritis, episcleritis, or orbital inflammation (3–5). Ocular symptoms are the first signs of GPA in only about 15% of cases (5). However, retinal vascular occlusions, particularly of the central retinal artery (CRA), are exceedingly rare but potentially sight-threatening complications, affecting less than 5% of patients (6).

The CRA includes the primary blood supply to the inner layers of the retina (7, 8). Occlusion of the CRA typically leads to acute, painless monocular vision loss and is considered a medical emergency. In most cases, CRAO is caused by embolic events or thrombosis but can also be related to vasculitic processes, particularly in autoimmune diseases like GPA (7, 8). In the context of GPA, vasculitis of the small vessels may contribute to CRAO (6).

This case report presents a rare manifestation of transient CRAO in a patient with GPA and highlights the challenges in diagnosing and managing ocular complications in patients with systemic vasculitis, and underscores the risk of inflammatory-mediated vascular occlusions in these patients.

CASE PRESENTATION

PATIENT HISTORY

A 49-year-old male with a 2-year history of GPA presented to our department with three episodes of, transient, painless monocular vision loss in his right eye, lasting a few seconds, consistent with amaurosis fugax, followed by complete recovery. There was no history of trauma, flashing lights, or floaters. He had never experienced similar symptoms in the past. His ocular history was insignificant.

At the time of presentation, the patient was hospitalized in the Pulmonology Department due to worsening of his pulmonary involvement with pleuritis. Thoracentesis revealed an exudative pleural effusion with a predominance of polymorphonuclear cells, negative cytology, and negative tuberculosis testing. Strongly positive classic Antineutrophil Cytoplasmic Antibody (c-ANCA) and elevated anti-proteinase 3 antibodies (anti-PR3) levels, in combination with renal involvement manifested by hematuria and proteinuria, as well as the patient's clinical features, were indicative of a flare of GPA. A nephrology consultation was obtained, and the renal findings were considered consistent with active c-ANCA-associated glomerulonephritis. No lung or renal biopsy was performed, as it was not deemed necessary given the characteristic clinical and serological profile strongly suggestive of pulmonary and renal involvement in a GPA flare. The patient had hypothyroidism and was a non-smoker. Lipid profile was within normal limits, and no additional cardiovascular risk factors were identified apart from arterial hypertension.

At initial GPA presentation two years earlier, the patient exhibited lower respiratory tract involvement characterized by pleural effusion, accompanied by migratory arthralgias and arthritis, vasculitic rash, febrile episodes, weight loss, and pericardial effusion with signs of right ventricular pressure overload without wall motion abnormalities; pulmonary embolism was excluded by Computed Tomography Pulmonary Angiography (CTPA). The diagnosis of GPA was established based on positive c-ANCA and elevated anti-PR3 levels in conjunction with characteristic clinical features, which obviated the need for histologic confirmation; thus, biopsy of the lung or other affected organs was not performed. No major relapses were reported before the current flare, and remission was achieved with low-dose glucocorticoids and methotrexate.

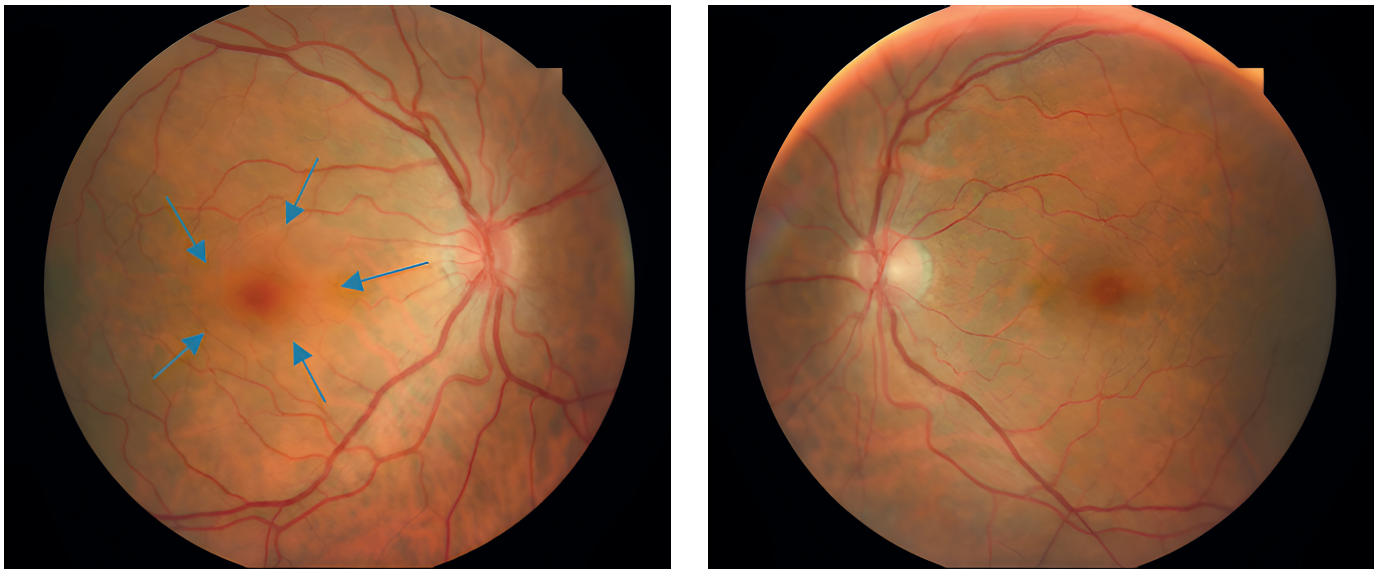

Fig. 1 Mild whitish hue of the macula in the right eye.

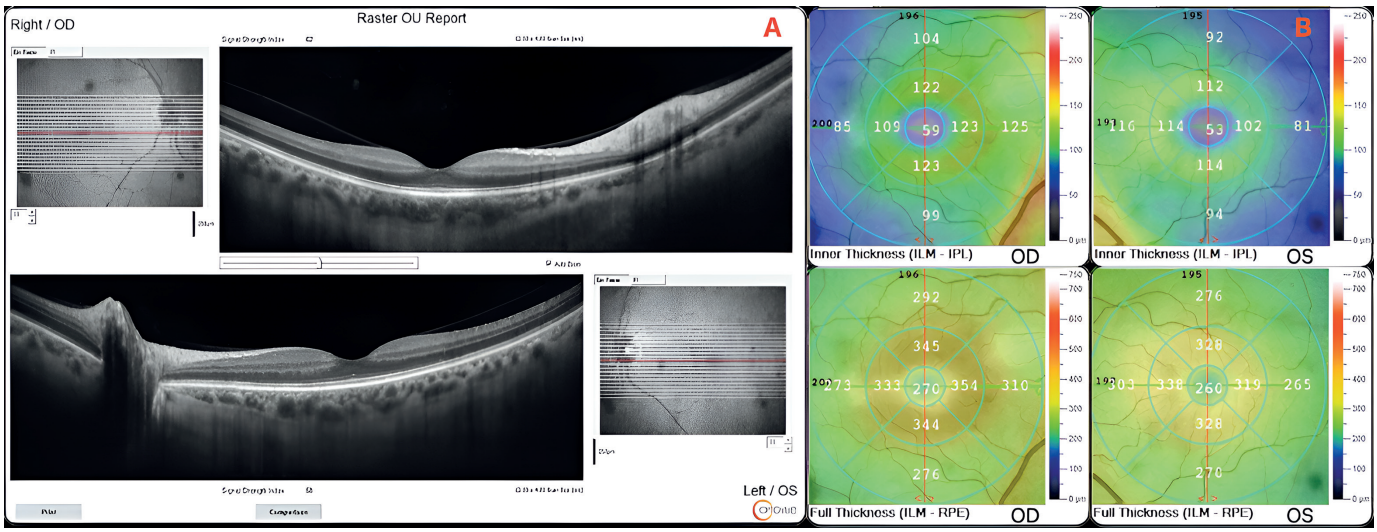

Fig. 2 A) OCT of the patient and B) Full and inner thickness maps showing thickening in the right eye.

PHYSICAL EXAMINATION

On presentation, the patient's vital signs were within normal limits. Best-corrected visual acuity (BCVA) in each eye was 20/20 (logMAR 0.0). Ocular motility was normal, and no RAPD was noted. Visual fields by confrontation were normal in both eyes.

Slit-lamp examination of the anterior segment was unremarkable. Dilated fundus examination of the right eye revealed areas of diffuse retinal ischemia with vascular attenuation and "box-carring" of flow in arteries and veins. The macula and optic disc showed no remarkable pathological signs. Left eye examination was unremarkable.

Shortly before the angiography, the patient experienced another episode of amaurosis fugax, which persisted for more than a minute, longer than previous episodes. Visual acuity in the right eye deteriorated to hand movements. Fundus examination revealed a mild whitish hue, which, in combination with the increased thickness of the inner layers in the macula, is indicative of ischemia due to CRAO (Figures 1 and 2).

DIAGNOSTIC WORKUP

Given the patient's known history of GPA, CRAO secondary to vasculitis was considered. However, other potential causes, such as embolic events, had to be ruled out. The patient underwent immediate investigations, including:

- **Optical Coherence Tomography (OCT):** There were no significant findings on b-scan but thickness maps showed full and inner retinal thickening in the right eye, probably due to ischemia secondary to CRAO (Figure 2).
- **Optical Coherence Tomography – Angiography (OCT-A):** OCT-A and enface OCT showed areas of non-perfusion in the superficial and deep capillary

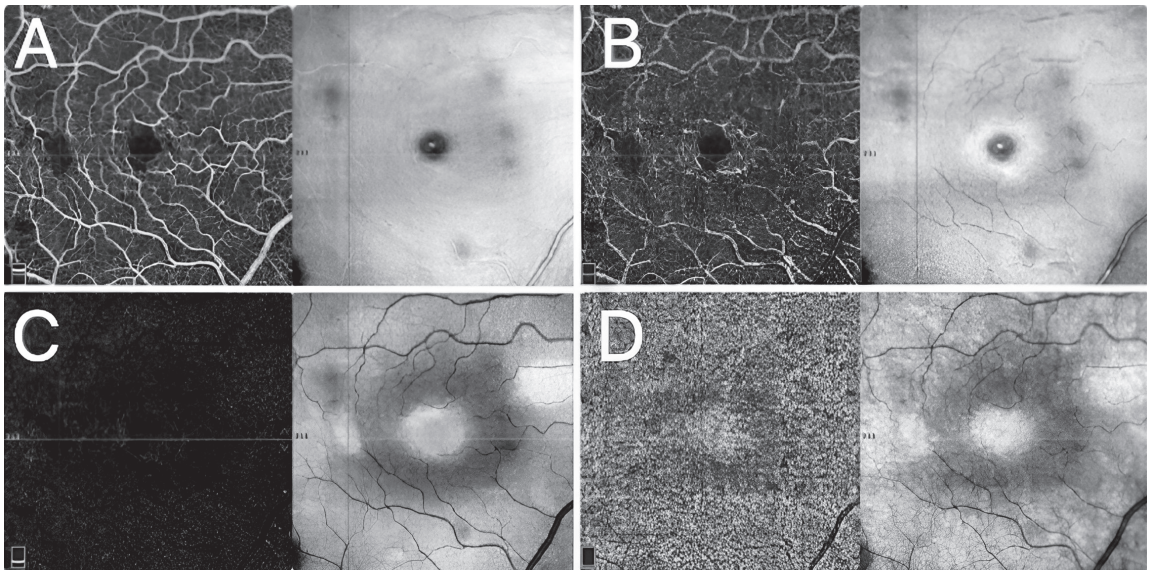

Fig. 3 OCT-A findings. A) Superficial and B) Deep capillary plexus abnormalities. C) Outer retina and D) choriocapillaris layers shadowing.

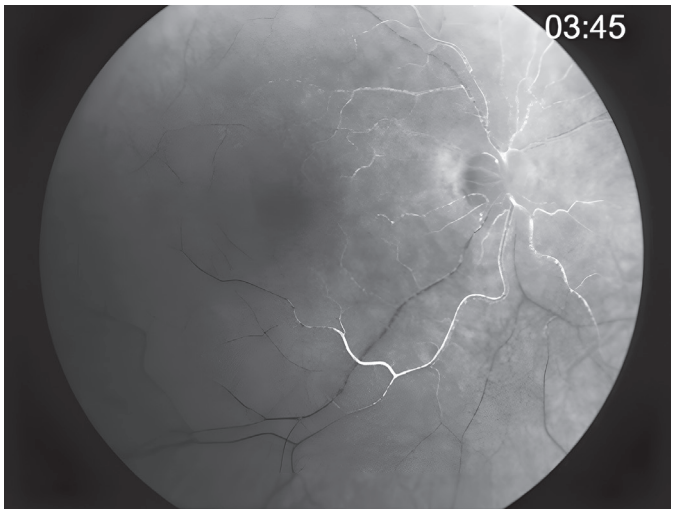

Fig. 4 CRAO signs in FA.

plexus (Figures 3A and 3B). Furthermore, shadowing to the outer retina and choriocapillaris layers due to edema in the inner retinal layers was revealed (Figures 3C and 3D).

- **Fluorescein Angiography (FA):** FA showed delayed filling of the central retinal artery, with normal choroidal circulation (Figure 4). No evidence of vascular leakage or emboli was observed, further supporting the diagnosis of CRAO due to vasculitis rather than an embolic event.
- **Complete Blood Count (CBC) and Erythrocyte Sedimentation Rate (ESR):** CBC was within normal limits, but ESR was elevated at 88 mm/hr, suggesting active inflammation.
- **C-reactive Protein (CRP):** CRP was also elevated, consistent with systemic inflammation (24 mg/L).
- **Serum Creatinine and Urinalysis:** Serum creatinine was elevated at 1.3 mg/dL, and urinalysis showed hematuria (10–20 red blood cells per high power field) and proteinuria (1.2 g/24h), raising concerns about renal involvement in the context of a GPA flare.
- **Serological Testing:** The patient was positive for c-ANCA and anti-PR3 with a high titer, which is characteristic of GPA. This finding, in combination with elevated inflammatory markers, suggested a GPA flare. A longitudinal representation of c-ANCA titers demonstrated elevated levels (1:160) at initial diagnosis, followed by a period of low titers after initiation of immunosuppressive therapy, consistent with disease remission. A subsequent rise in c-ANCA levels was observed at the time of clinical exacerbation (1:80) (Figure 5), supporting the association between systemic disease activity and retinal vascular occlusion. Anti-PR3 levels followed a similar trend, with elevated values at diagnosis (216 IU/mL) and relapse (244 IU/mL).

DIAGNOSIS

The patient was diagnosed with transient central retinal artery occlusion secondary to a flare of GPA-related vasculitis. The diagnosis was based on clinical presentation, history of GPA, elevated inflammatory markers and the absence of emboli on fluorescein angiography.

MANAGEMENT

Given the acute nature of CRAO and the risk of permanent vision loss, immediate treatment was initiated. The patient was admitted for aggressive immunosuppressive therapy to control the GPA flare and prevent further vascular complications.

First Line Therapy

- **Anticoagulation and Vasodilators:** Although embolic causes were ruled out, low-dose aspirin was prescribed as a preventive measure. Topical vasodilators and ocular massage were attempted to improve retinal

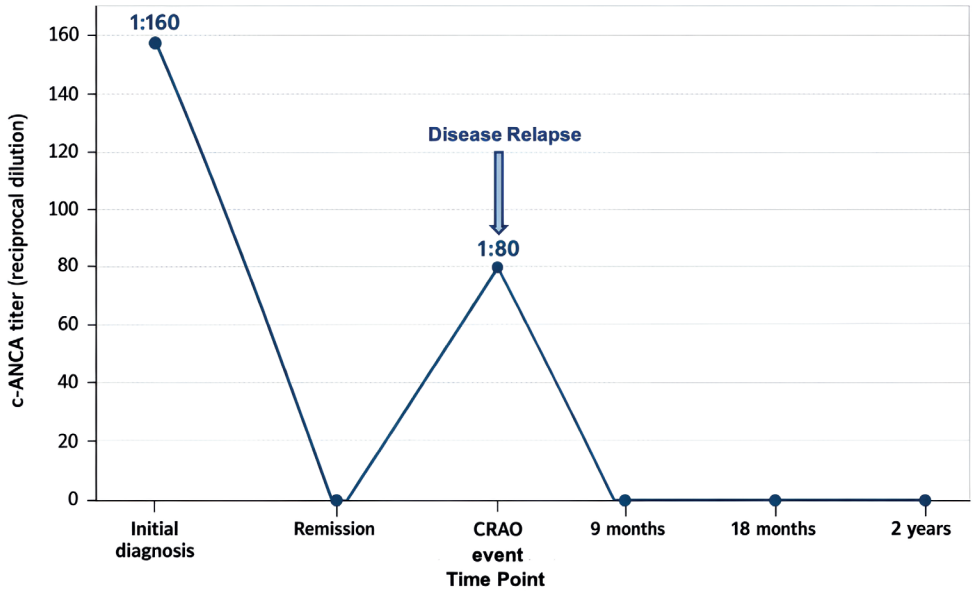

Fig. 5 Longitudinal changes in c-ANCA titers. c-ANCA titers decreased from 1:160 at initial diagnosis to undetectable levels during remission, followed by a rise to 1:80 at the time of disease relapse associated with CRAO. Subsequent measurements remained undetectable throughout follow-up. Titers are expressed as reciprocal dilution values.

perfusion, although these measures have limited efficacy in CRAO (8).

Systematic Therapy

- **High-Dose Glucocorticoids:** The patient was started on intravenous methylprednisolone (1 g/day) for three days, followed by oral prednisone and taper off.
- **Immunosuppressive Therapy:** Methotrexate was discontinued, and rituximab was introduced as a more effective long-term therapy for GPA management.

OUTCOME AND FOLLOW-UP

Within 30 minutes of the aforementioned treatment (anticoagulation and vasodilators), the patient reported full recovery of vision in his right eye.

Within 24 hours of initiating treatment, BCVA remained stable at 20/20 (logMAR 0.0), and fundus examination revealed regression of CRAO signs. No further amaurosis fugax episodes were reported.

After one week of corticosteroid therapy, the patient's BCVA remained stable at 20/20 (logMAR 0.0). The patient was discharged on a maintenance dose of oral prednisone and rituximab infusions every six months.

At the three-month follow-up, no further evidence of vasculitis was noted, and ANCA levels had decreased. Repeat OCT showed normal thickness of the inner retina. (Figure 6). FA showed normal filling of the retinal vessels. Fundus examination was unremarkable.

At the two-year follow-up, the patient remained clinically stable with no signs of recurrent vasculitis. c-ANCA levels were negative (Figure 5), and no further episodes of amaurosis had been reported.

DISCUSSION

This case highlights a rare but serious ocular complication of GPA, transient CRAO. Retinal artery occlusions in the context of GPA are exceedingly rare and are typically associated with active vasculitis, as demonstrated in this case report. Early recognition and aggressive immunosuppressive treatment are crucial for avoiding vascular occlusive events.

Ocular involvement in GPA most commonly manifests as scleritis or orbital inflammation, but retinal vascular occlusion can occur in severe cases of vasculitis (3–5). The pathophysiology involves immune-mediated inflammation of small blood vessels, leading to vessel wall damage, inflammatory thrombus formation, and subsequent ischemia. In this case, the patient's elevated inflammatory markers and positive c-ANCA and anti-PR3 titers suggested a systemic vasculitis flare, which likely contributed to the transient CRAO (9, 10). Indeed, despite initial treatment with methotrexate, the patient experienced disease relapse, highlighting that this agent may be insufficient to maintain remission in certain cases of granulomatosis with polyangiitis. Consequently, therapy was escalated to

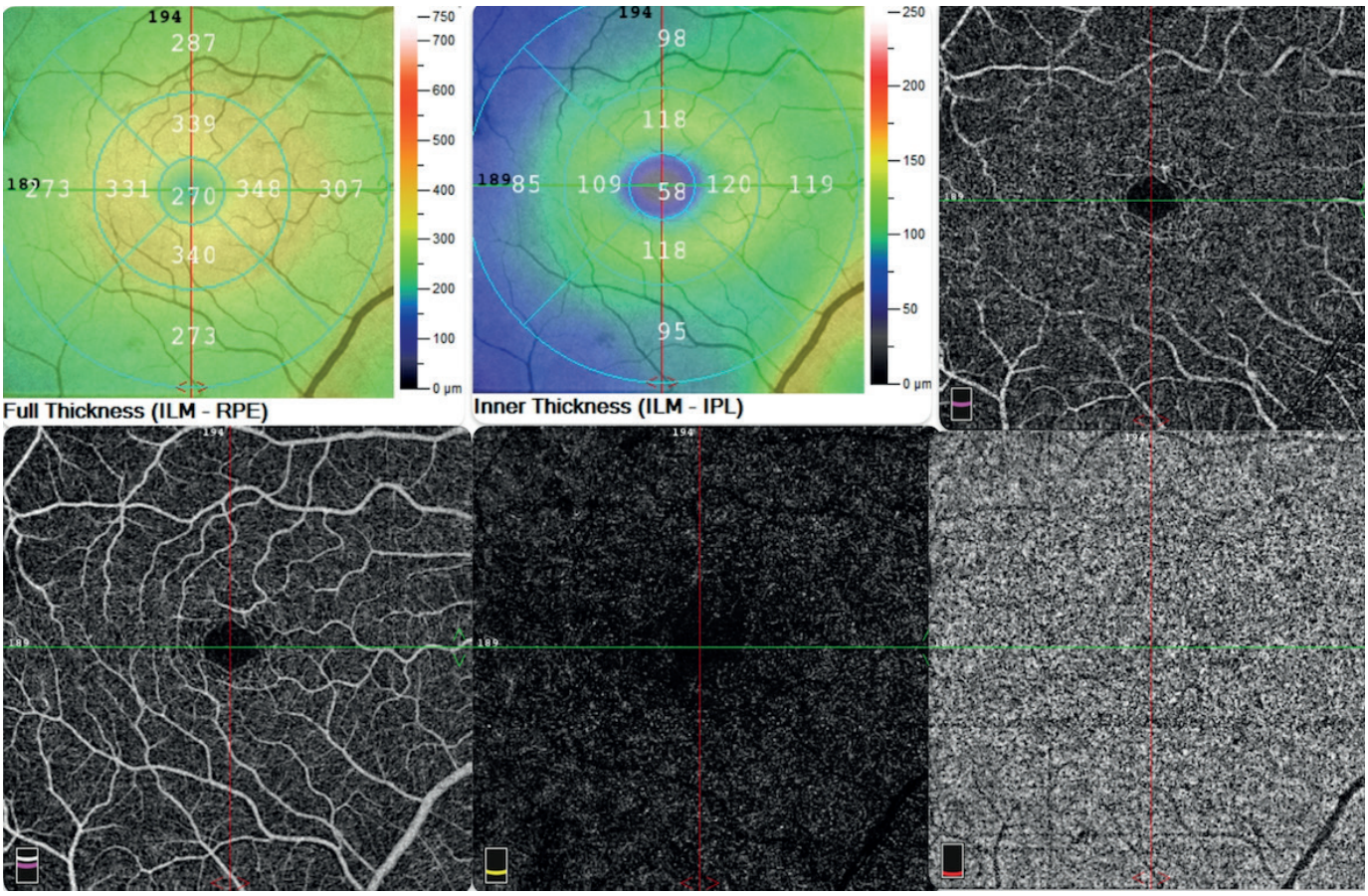

Fig. 6 Thickness maps and OCT-A at three-month follow-up.

rituximab, reflecting the need for more potent immunosuppression in the setting of disease reactivation.

In the present case, no histopathological confirmation was obtained, as biopsy was not deemed necessary at either the time of initial diagnosis or during disease relapse. This decision was based on the presence of a highly characteristic clinical presentation in combination with supportive laboratory findings, including positive c-ANCA and anti-PR3 serology, which together provided sufficient diagnostic confidence for granulomatosis with polyangiitis.

A thorough literature review revealed that cases of CRAO associated with GPA are extremely rare in the English literature. The limited number of published cases suggests that CRAO typically occurs in the setting of active, systemic disease, often accompanied by other manifestations such as renal, pulmonary, or ear, nose, and throat (ENT) involvement (11). In comparison to the existing literature, our case shares several overlapping features, including the presence of active vasculitic disease and elevated c-ANCA titers at the time of ocular presentation.

Furthermore, previously reported cases emphasize the importance of early immunosuppressive treatment, as visual prognosis following CRAO is generally poor despite prompt intervention (11). In contrast to these reports, in our case, immediate management was associated with a transient occlusive event, without recurrence during follow-up. This observation reinforces the importance of heightened clinical suspicion and early intervention when patients with known or suspected GPA present with acute visual symptoms (9).

To our knowledge, this is the first case report that includes a comprehensive diagnostic workup, including FA, OCT and OCT-A findings, and demonstrates full vision recovery (9, 12).

STATEMENT OF ETHICS

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

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