International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

IJAMSCR|Vol.14 | Issue 4 | Oct - Dec -2025

www.ijamscr.com

DOI : https://doi.org/10.61096/ijpar.v14.iss4.2025.737 -749

ISSN: 2347-6567

Research

CURRENT DEFICIENCIES IN SCHEDULE Y

K. Pallavi[1*], Ch. Sunitha[2], Dr. l. Harikiran[2]

[1,2] Department Of Pharmaceutical Regulatory Affairs, Princeton College Of Pharmacy In Narapally, Ghatkesar, Telangana.

[*]Author for Correspondence: K. Pallavi
Email: princeton.pharmacy@gmail.com

Published on:

Published by:
Futuristic Publications

2025| All rights reserved.

Creative Commons Attribution 4.0 International License.

Abstract

To investigate "up-to-date" and "age-appropriate" indicators of preschool vaccination status and their implications for vaccination policy. The authors analyzed medical records data from the Baltimore Immunization Study for 525 2-year-olds born from August 1988 through March 1989 to mothers living in low-income Census tracts of the city of Baltimore.While only 54% of 24-month-old children were up-to-date for the primary series, indicators of up-to-date coverage were consistently higher, by 37 or more percentage points, than corresponding age-appropriate indicators. Almost 80% of children who failed to receive the first dose of DTP or OPV age-appropriately failed to be up-to-date by 24 months of age for the primary series.Age-appropriate immunization indicators more accurately reflect adequacy of protection for pre schoolers than up-to-date indicators at both the individual and population levels. Age-appropriate receipt of the first dose of DTP should be monitored to identify children likely to be under immunized. Age-appropriate indicators should also be incorporated as vaccination coverage estimators in population-based surveys and as quality of care indicators for managed care organizations. These changes would require accurate dates for each vaccination and support the need to develop population-based registries.

Keywords: Immunization Study, DTP, OPV, vaccination

INTRODUCTION

The growing prevalence of obesity[1], combined with the absence of effective conservative treatment [2] and probably with the development of laparoscopic surgery, has led to a significant increase in the number of bariatric surgical procedures performed each year in most Western countries [3]. Bariatric surgery has been shown to produce effective

and sustainable weight loss, which in turn results in improvement of obesity-related comorbidities, of quality of life, and of survival [4].

Gastric banding and Roux-en-Y gastric bypass (RYGBP) are currently the most commonly performed surgical procedures for morbid obesity [body mass index (BMI; in kg/m2) >40]. Laparoscopic gastric banding is a purely restrictive procedure. It has a low operative morbidity but is associated with a substantial rate of late complications and failure[5,6]. Laparoscopic RYGBP is essentially restrictive, but in contrast with gastric banding, it is associated with nutritional deficiencies and has a higher operative morbidity[7]. However, it represents the procedure of choice for many surgeons[8,9] because it induces greater weight loss with better food tolerance.

After RYGBP, careful follow-up is needed to detect and correct nutritional deficiencies. Unfortunately, data about the type and the frequency of these postoperative deficiencies remain scarce[10,11].

The aims of this retrospective study were

1) To assess the type, frequency, and pattern of development of nutritional deficiencies over the first 24 months after RYGBP,

2) To determine the amount of supplements prescribed to each patient,

3) To evaluate the cost of the substitutive treatment.

This information is important to standardize postoperative follow-up and to define which type of nutritional substitution has to be prescribed after RYGBP. It will allow a reduction of the frequency and the consequences of nutritional deficiencies and a decrease in health care–related costs.

Incorporating the patient experience into the clinical decision-making process is of increasing interest to the international regulatory and health policy community,[12] as these bodies increasingly recognize that patients are experts in terms of their preferences and have a unique knowledge of their own health. The patient experience can be captured in a number of different ways; an increasingly important approach is via patient preference (PP) studies.

PP studies generate rigorous data on patients' perception and preferences surrounding different aspects of existing or investigational health-related products, services, and interventions. The growing use of PP studies helps incorporate the patient perspective into clinical drug development, care management, and the broader healthcare decision-making of regulators and payers.[13-17] Over the last decade, benefit-risk methodologies have evolved substantially and are seen by regulators and industry stakeholders as a valuable tool in aiding transparency and communication in decision-making. Benefit-risk evaluation is both subjective and objective, and PP data can help regulatory and other stakeholders (eg, payers) evaluate and communicate value-based judgments.

Preference research allows estimation of the relative importance of different aspects of care, the trade-offs between these aspects, total satisfaction or utility that respondents derive from healthcare services and can help with decision making for some of the important issues in healthcare.

As summarized in the US Food and Drug Administration (FDA)'s "Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labelling" guidance, patient preference data may be collected through qualitative or quantitative approaches. There are several quantitative approaches to eliciting patient preference data; some use revealed-preference methods (whereby patient preferences are obtained from actual observed choices made by participants), while others use stated-preference methods (in which preferences are elicited by offering choices to participants). A discrete choice experiment (DCE) is a quantitative stated-preference method for eliciting preference data. DCEs are based on random utility theory (RUT), a long-standing theory of choice behaviour proposed by Thurstone in 1927.[18,19] The method involves presenting participants with a choice task that requires a force choice between hypothetical alternative products (or programs, or services). Participants are asked to state their preference from the alternative options. These data are used to evaluate how respondents' value selected attributes of a product (or program or service), whether preferences are influenced by the attributes, and the relative importance of the attributes.[20]

Growth hormone deficiency (GHD) in adults and children has been treated over the last several decades with recombinant human growth hormone (r-hGH) administered as a daily injection. Whilst this treatment has, on the whole, been successful, evidence indicates that adherence with daily treatment is less than optimal[21] and presents a

particular challenge in children for a variety of reasons (including discomfort or pain with daily injections, the required length of treatment, and the patients and parents understanding of treatment benefit and consequences of non-compliance).[22,23] The psychological impact on the family, and in particular the impact on the caregiver who primarily administers the daily injections to young children, can be emotionally distressing.

It has been hypothesized that a less frequent injection schedule (for example, a weekly or monthly injection schedule) could improve patient adherence.[24] In children, this would obviously result in improved long-term height outcomes and improved quality of life (QoL). Injection frequency for administration of r-hGH injections may be an important factor for patients and clinicians when initiating therapy for GHD and making subsequent treatment choices for this chronic condition. Various delivery and device attributes (ie, product features such as safety, effectiveness, or mode of administration) may factor into patient preferences about r-hGH injections, such as frequency, device, and storage options. Little research regarding r-hGH injection frequency preferences has been done to date, since the development work on these newer "less frequent" products is still ongoing, and they are not currently available for routine prescribing.

The goal of this study was to ascertain relative patient preferences associated with the r-hGH injections and injection devices using DCE methods.

Screening of medical records and patient selection

This study was a retrospective analysis of medical records of obese patients who underwent bariatric surgery by RYGBP at our centre. Only patients who complied with our follow-up schedule (see below) during the first 2 y after surgery were included. We excluded from our analysis

1) Patients who underwent RYGBP secondarily after having previously undergone another bariatric procedure,

2) Patients who were lost to follow-up or who attended <4 of the planned medical visits during the first 2 y after RYGBP,

3) Patients whose blood analyses were performed in outside laboratories,

4) Patients who became pregnant during the first 2 y after RYGBP

5) Patients who were treated with nutritional supplements before RYGBP.

Surgical technique

The surgical technique was described in detail elsewhere. The length of the Roux-en-Y limb was determined by the patient's BMI; it was 100 cm for those with BMI ≤ 48.0 and 150 cm for those with BMI > 48.0. Cholecystectomy was performed if gallstones were present and in many of the remaining patients as prophylaxis against the occurrence of gallstones during rapid weight loss. All patients included in the analysis were operated on between November 1999 and June 2004.

Clinical and biologic follow-up

Every patient met a physician of our team at least once before surgery; after surgery, they were seen every 3 Mo during the first postoperative year and at 6-mo intervals during the second year. Height was measured at the preoperative consultation with the use of a studio meter. At each consultation, body weight was measured using a Detector scale (Detector, Webb City, MO), and BMI was calculated. The percentage of excess body weight was calculated according to the ideal body weight.

At each postoperative consultation, a non fasting blood sample was drawn. Measurements included total and corrected calcium, albumin, parathyroid hormone, 25-hydroxyvitamin D, iron, ferritin, folic acid, erythrocyte magnesium, zinc, and vitamin B-1, B-6, and B-12 concentrations and a complete blood count. All biochemical analyses were performed by certified laboratories (ISO CEI 17025) and run in duplicate or triplicate samples. Normal reference ranges and techniques used by our laboratory for the measurement of several vitamins and micronutrients.

AIM AND OBJECTIVE

The aims of this retrospective study were

1) to assess the type, frequency, and pattern of development of nutritional deficiencies over the first 24 mo after RYGBP,

2) to determine the amount of supplements prescribed to each patient,

3) to evaluate the cost of the substitutive treatment.

DISCUSSION

RYGBP has become one of the most common bariatric procedures. However, long-term nutritional outcome data remain scarce, and, aside from a few published expert recommendations, there are no guidelines regarding the optimal postoperative nutritional follow-up. The aim of this study was to improve our knowledge of the nutritional consequences of RYGBP, because of potential complications related to development of nutritional deficiencies such as neurologic dysfunction for vitamin B-12 deficiency.

Our main observations are as follows. *1*) Standard multivitamin supplementation is not sufficient to prevent nutritional deficiencies after RYGBP. Indeed, almost 60% of our patients required one or more nutritional supplements 6 mo after surgery, with virtually all patients needing them after 2 y. *2*) The prevalence of vitamin D and calcium deficiency increases significantly with the length of the Roux-en-Y limb. *3*) Proper postoperative nutritional substitution can become a burdensome and expensive treatment, which may challenge a patient's compliance considerably.

The reported incidence of specific deficiencies after RYGBP varies widely in the current literature: between 10% and 50% for vitamin B-12 and iron and between 0 and 40% for folic acid. Hypovitaminosis D with secondary hyperparathyroidism was found in up to 80% of patients both pre- and postoperatively. No data are available for vitamins B-1 and B-6, magnesium, and zinc. However, most authors report the incidence of specific deficiencies at different time points after surgery, without considering the number of patients who will require any substitutive treatment during follow-up. In addition, some authors prescribe a multivitamin supplement immediately after RYGBP and others do not, potentially confounding the data. Finally, the time points at which patients are studied vary among studies, and yet, as exemplified by the present data, the prevalence of nutritional deficiencies increases with time. We chose here to report the proportion over time of patients receiving one or more nutritional supplements. Because these supplements were prescribed according to strict guidelines on the basis of regular biologic measurements, we believe that these data provide an accurate picture of the clinical importance of this problem over the period under study. By reporting the mean number of supplements prescribed for each patient, our study is also the first to illustrate the burden of nutritional substitution.

Despite some limitations inherent to the retrospective design of this study, our data stress the fact that oral and/or parenteral nutritional supplementation can become a potential problem for patients. Indeed, they demonstrate that a standardized multivitamin supplement with a single pill per day will probably not meet the needs of the vast majority of patients. Taking several pills a day raises the problem of adherence to treatment. The cost of treatment can be another barrier to adequate compliance. Our estimates show that 2 y after RYGBP, a patient will have to spend on average $35 per month for his or her nutritional supplements, an amount high enough to impair compliance in a significant proportion of patients in countries in which health insurance companies do not cover these costs. This situation is well illustrated by a study reporting that in a group of 348 patients treated by RYGBP, only 33% complied with the multivitamin regimen throughout the study period. This dramatically low adherence rate suggests that appropriate compliance should regularly be assessed and encouraged during the postoperative follow-up. Finally, costs related to extensive biologic nutritional assessment are also high, averaging $360 per patient per sample at our center or $2100 for the 6 blood samples obtained during the entire follow-up period. Although the cost-benefit ratio of this follow-up should be formally evaluated, our data stress the need for a carefully planned postoperative follow-up, taking into account potential benefits to the patients as well as health care–related costs.

Because all patients received a multivitamin supplement between months 1 and 6 after RYGBP, the real incidence of nutritional deficiencies during this period probably cannot be extrapolated from the present data. However, prescribing a multivitamin supplement after RYGBP is a commonly used procedure, and therefore these results may be a better reflection of what would be found in other clinics using similar treatment plans. We also did not seek information about the preoperative nutritional status of our patients, and deficiencies recorded during follow-up may

possibly represent problems existing before the surgical procedure. However, most deficiencies occurred after the sixth postoperative month, suggesting that they were not present before surgery.

In consideration of the high prevalence of nutritional deficiencies, the relative rapidity of their appearance after RYGBP, the lack of effectiveness of multivitamin supplementation, and the high cost of the above-mentioned postoperative follow-up, an achievable alternative to our follow-up schedule and treatment plan would be to prescribe vitamin B-12, iron, calcium + vitamin D-3, and folic acid supplements in sufficient amounts to all patients after RYGBP. A pragmatic approach of prescribing a double dose of a multivitamin is sometimes used; however, the effectiveness of this approach has not yet been fully demonstrated. Therefore, the development of a single "multi-pill" or injection containing appropriate doses of vitamin B-12, iron, calcium + vitamin D-3, and folic acid would facilitate compliance and reduce costs; research to determine the proper dosage and route of administration of this type of medication should be encouraged. With such a regimen, our data suggest that nutritional assessments performed every 6 mo would be adequate to both detect less frequent deficiencies such as those of vitamins B-1 and B-6, zinc, or magnesium and monitor the efficacy of treatment.

RYGBP has become one of the most commonly performed bariatric procedures. Our data demonstrate that after surgery routine supplementation with a standardized multivitamin preparation alone does not prevent the frequent occurrence of nutritional deficiencies. We therefore suggest that rigorous postoperative follow-up should be implemented in all patients to detect the most frequent of these deficiencies, which include deficiencies of vitamin B-12, iron, calcium, 25-hydroxyvitamin D, and folic acid. Given the prevalence and clinical importance of this problem, prospective studies should be performed to establish formal guidelines for the nutritional care of these patients.

We express our deep gratitude to François Pralong, who offered his help by revising the manuscript.

The author's responsibilities were as follows—CG: collected and analyzed data, interpreted results, and wrote the manuscript; MS: participated in data collection and revised the manuscript; RG: revised the manuscript; and VG: participated in data collection, interpreted results, and wrote the manuscript. None of the authors had a personal or financial conflict of interest.

This DCE study was designed to estimate the relative importance and preferences for different aspects of the growth hormone injection device's use and handling. This patient preference study is the first study that we are aware of to evaluate patient preference for GH injections in this way. The strength of this DCE enabled an exploration of preferences relating to alternative options for delivery of r-hGH which are not currently available.

The focus of the study was on the degree to which each attribute contributed to the desirability of a pen device, rather than whether a particular device configuration would actually be used (or would be more preferable compared to existing options). This study, involving children, adolescents (and their caregivers) and adults yielded several results of interest. Overall, respondents indicated a clear preference for a less frequent injection schedule rather than daily injections (i.e., a preference for weekly, bi-monthly or monthly injections). This attribute was more important relative to others.

The study also included a separate exercise looking at the uptake of whether the participant would choose to switch from their current daily pen device, if given the chance, to a less frequent injection schedule. The results show that the vast majority of respondents would switch to a less frequent injection administration (weekly, biweekly or monthly, although there appeared to be slightly less support for a schedule given once every two weeks).

The results for each age category (children, adolescents and adults) are generally consistent. However, results indicate that adolescents showed a greater tendency to switch to a less frequent injection schedule compared to the adult and Pediatric cohorts. This is perhaps unsurprising, as evidence suggests that adherence to treatment in this age group reduces. Hence, the availability of an injection pen which requires only a once-weekly injection, or even fewer administrations, could offer patients a valuable option which could improve adherence and persistence, with potential clinical implications for improved growth outcomes.

The lower preference for a less frequent injection schedule seen in our adult cohort is aligned with a recent publication which also reported that adult patients were less likely to switch to a weekly injection schedule. The Amereller study suggests that if patients were provided with additional information regarding the efficacy and safety of a newly introduced product, patients may be more willing to switch when they are offered a choice between weekly and daily injection schedules.

DCE studies have some limitations. The potential for hypothetical bias is a general concern. Choices involving hypothetical treatments do not have the same clinical, financial and emotional consequences of experiencing the actual treatment. Hence, differences may arise between patients stated and actual choices. In this study, all respondents had considerable experience treating their GHD with daily injections; none of the respondents had experience or knowledge of alternative injection schedules.

All recruited participants were enrolled exclusively from clinics in the US, and while treatment for GHD is standard across different countries and regions, and therefore bias should be minimal, in an ideal scenario, patient preferences from other countries should also have contributed to these results. While patients in transition were excluded from this study, future research should explore the experiences of these patients.

Whilst the authors identified the attributes via internal consultation and previous research, the attributes identified and evaluated had not been robustly researched via a literature review and this could also be considered a limitation of the study. However, it is unlikely that a key attribute had been omitted. Attributes in DCE studies are always pre-defined and therefore it is possible a more relevant attribute may have been missed, but this is a limitation of all DCE studies.

One strength of the recruited sample is that since all respondents had participated in a broader clinical study we can be assured that everyone had been confirmed with a diagnosis of GHD. All participants in the clinical study participated in the conjoint analysis, with no drop outs – suggesting completion was not burdensome or challenging.

The attributes and scenarios applied in this study were tested in a set of 10 pilot interviews, during which respondents completed the online DCE exercise while a moderator observed them completing the exercise via screen share. During and after the exercise, the moderator asked the respondent targeted questions to ensure they understood the content and options presented. The results of this pilot study indicated that the attributes and scenarios were tangible and easily understood by respondents, so it is unlikely to have led to misunderstandings or lack of comprehension which may have led to varying interpretations of the data.

In conclusion, the voice of the patient and patient preferences regarding novel and different treatment options is becoming increasingly important to many stakeholders, in particular regulators who are interested in how these studies may best support the benefit/risk analysis of a new drug. In this study, the DCE was successful in evaluating the trade-offs and preferences patients with GHD and caregivers (dyads), when appropriate, were willing to make amongst injection pen attributes. The findings from this study suggest that a less frequent injection schedule is the most preferred and important attribute for patients with GHD. Less frequent injection schedules may be an important factor to improve compliance in this therapy area, which would lead to improved outcomes in the longer term. A recommended next step would be to conduct a randomized clinical trial, and ideally a real-world data study, to scientifically and robustly determine the clinical implications of a less frequent injection regimen.

These results do not support the hypothesis that a defect in the NPY system is mediating the decreases in intake during zinc deficiency. Concentrations of NPY in the PVN and NPY mRNA in the ARC were higher in Zn0 than in Zn/ rats. This difference appeared to be related more to decreased food intake than zinc deficiency because pair-fed rats exhibited similar increases in NPY concentrations. Reported that both NPY peptide and mRNA concentrations were increased in food-restricted rats. The present data are consistent with the recent report of with respect to NPY mRNA levels, but are not consistent with their report that NPY content is not different in Zn0 vs. Zn/ rats. However, we utilized PVN micro dissected from the hypothalamus, whereas measured levels in the whole hypothalamus. NPY content in the PVN and NPY mRNA levels in the ARC generally change in parallel, although there are a few examples of NPY content and gene expression not correlating.

There was no impairment in the feeding response to exogenous NPY in Zn− rats. At the highest dose of NPY (160 pmol) administered in this study, energy intake per kilogram body weight did not differ in Zn+ and Zn− rats. This observation contrasts with two previous studies in which exogenous infusions of orexigenic agents were administered centrally to Zn− and Zn+ rats. In those studies, it was observed that Zn− rats were resistant to increases in intake when dynorphin and norepinephrine, muscimol, and bromerogocryptine were administered. Because the four compounds tested by Essatara and colleagues did not equalize intakes of the groups, one hypothesis they advanced was that receptor function or sensitivity was reduced by zinc deficiency. In this study, equivalent energy intake in Zn− and Zn+ groups when 160 pmol of NPY was infused suggests that NPY receptor function may not be compromised by zinc deficiency. It is not practical to include a pair-fed group of rats in short-term intake studies because pair-fed rats are voracious eaters and consume food almost continuously for an hour or more upon

presentation of diet. Our preliminary tests demonstrated that intakes of PF rats were unaffected by treatment (data not shown). Did not use pair-fed rats for the same reason. A discussion of the range of problems encountered with pair-fed rats in zinc deficiency studies is presented by O′Dell and Reeves (1989).

It may be that during zinc deficiency, the NPY neurons extending to the PVN are less able to process NPY into its final, fully active form. Zinc deficiency impairs processing of the brain peptide, thyrotropin-releasing hormone. Incompletely processed NPY has a lower affinity for NPY receptors, and the amidated C-terminal end of the NPY peptide interacts with NPY receptor binding sites. During zinc deficiency, the hypothalamus may be normally responsive or even hyper responsive to infusions of NPY. We suggest that this could occur during zinc deficiency if less than normal amounts of NPY are being released from terminals within the PVN or if incompletely processed pro-NPY peptide is being released from cells. This hypothesis does not agree with the current results indicating higher, rather than lower concentrations of NPY during zinc deficiency, although the assay used in this study detects total NPY immunoreactivity and does not measure the various processed forms of NPY. Another study reporting increases in in vitro NPY secretion during zinc deficiency (Tovar-Palacio et al. 1996) also used an assay that did not measure processed forms of NPY.

The hypothesis that zinc deficiency–induced anorexia is related to decreases in NPY now appears less likely. The increase in NPY during zinc deficiency appears to result from the reduced intake of Zn− rats. The parallel increase of NPY content and NPY gene expression associated with zinc deficiency may be a normal regulatory response made in an attempt to increase intake in Zn− rats. Yet, while consuming a Zn− diet, these rats continued to eat less, unlike food restricted rats. Because Zn− rats increase food intake after infusion of exogenous NPY and are at least as responsive as Zn+ rats to similar infusions, the NPY system appears to be intact postsynaptically. If the processing of NPY is unaffected by zinc deficiency, then on the basis of these results, it appears likely that some other physiologic change is mediating this anorexia.

The main finding of the IIISAS trial was that treatment with ferric derisomaltose did not provide benefit beyond TAVI in terms of 6-min walk distance (*Graphical Abstract*), NYHA class, muscle strength, or quality of life in iron-deficient patients with severe aortic stenosis. Intravenous iron led to repletion of iron stores in 79% of the patients and except for one hypersensitivity reaction which resolved quickly after adequate treatment, the treatment was safe.

In patients with heart failure, iron deficiency regardless of haemoglobin status is a recommended treatment target based on the results of randomised trials. In patients with severe aortic stenosis, only a few studies have examined the association between iron deficiency regardless of haemoglobin levels and adverse events following TAVI In an observational study on 495 patients undergoing TAVI, preprocedural iron deficiency was associated with adverse outcomes after TAVI. In a subgroup of patients ($n = 56$), intravenous iron resulted in improvements in both iron markers and symptoms at 30-day follow-up. Consequently, many have emphasized the need for clinical trials to investigate the potential benefit of intravenous iron in patients with severe aortic stenosis.

The IIISAS trial included patients with iron deficiency, but only a few patients had anaemia, and severe anaemia was an exclusion criterion. Consequently, it cannot be concluded that intravenous iron does not have a position in the treatment of anaemic patients with severe aortic stenosis. However, prespecified subpopulation analyses on patients with and without anaemia indicated no benefit in anaemic patients. This suggests that anaemia and iron deficiency may serve as markers of poor outcomes, rather than cause these outcomes. Frailty is a multidimensional, dynamic state that makes the individual more vulnerable to the effect of stressors. Aortic stenosis and frailty are two distinct yet commonly associated conditions, and the presence of frailty in patients undergoing TAVI is associated with adverse outcomes.

To assess the effect of one intervention when the patient undergoes another intervention is challenging. TAVI is a complex procedure that can be associated with severe complications. On the other hand, the benefit provided by successful intervention may eclipse the potential benefits of intravenous iron in the preoperative setting. In our population, the success and complication rates following TAVI were comparable between the two treatment arms. The relatively high drop-out rate is also a relevant issue. However, the similarities between the patients who were excluded from and included in the modified intention-to-treat population and the fact that imputation analyses did not change the results increase the robustness of the findings despite the drop-outs.

The overall change in the 6MWT after TAVI was moderate and 38 patients failed to improve their 6-min walk distance after TAVI. These results are comparable to those found in a recent study on patients who performed a 6MWT before and 6 months after TAVI. In this study, the sub-group of 152 ‘fast walkers’, who had a baseline walk

distance that was comparable to that of our population, improved their walk distance by a mean of 20 m. The limited effect of TAVI on the 6-min walk distance raises the question of whether any intervention can be expected to improve the 6-min walk distance in a contemporary population of patients with severe aortic stenosis. The NT-proBNP levels in our population were moderately elevated, consistent with the low EuroSCORE and the inclusion criteria requiring a minimum 6-min walk distance of 100 m.

The IIISAS trial screened consecutive patients with severe aortic stenosis who were evaluated for TAVI and confirmed the high prevalence of iron deficiency observed in two previous studies. The administration of intravenous iron led to repletion of iron stores in most patients (76%), suggesting that the missing effect on clinical endpoints was not caused by inefficient treatment of the pre-existing iron deficiency. We have no reason to believe that the blood transfusions administered during TAVI substantially affected the iron parameters measured 3 months after TAVI.

Whether the definition of iron deficiency applied in patients with heart failure is valid in patients with severe aortic stenosis has not been investigated. A TSAT <20% is useful to define low plasma iron availability to tissues in iron deficiency. Little evidence is available from high-quality studies to justify specific thresholds for serum ferritin. However, clinical trials have proved that the cut-points used in heart failure are clinically useful in this condition, and consequently, they are now largely accepted. Further investigation is warranted to determine optimal cut-off values for iron deficiency in patients with severe aortic stenosis. In our trial, however, there were no signals towards a benefit of treatment in the prespecified subgroups with either ferritin <30 µg/L or in the patients with TSAT <20%.

Across the treatment arms, the TAVI procedure improved quality of life, NYHA class, and 6-min walk distance 3 months after TAVI. However, the results of our proof of concept trial do not provide support for routinely administration of intravenous iron to improve these outcome measures in patients with severe aortic stenosis and iron deficiency scheduled for TAVI. Except for one hypersensitivity reaction, the administration of intravenous ferric derisomaltose was safe.

This study is the first to define preoperative micronutrient status in an African patient cohort scheduled for metabolic surgery. In South Africa, literature is available on the baseline patient profiles and outcomes after metabolic surgery, but little is known about the preoperative micronutrient status of bariatric cohorts. This study, in predominantly morbidly obese females, revealed significant deficiencies of some micronutrients at baseline indicative of obesity as a state of excess energy and is not synonymous with optimal nutrition. Like data from the developed world, vitamin D deficiency (57%) was the most prevalent, followed by iron deficiency (44%) and then folate deficiency (18%); with 88% (136/154) of the participants having at least one nutrient deficiency prior to surgery. Identification of the most prevalent micronutrient deficiencies preoperatively, enables clinicians to limit laboratory measurements in a resource constrained setting. The results suggest that the preoperative assessment of individuals scheduled for metabolic surgery should include, at minimum, the measurement of 25(OH)D, iron studies and folate.

While initial thinking framed obesity as a disease of the developed world, evidence indicates that the developing world is equally, if not more, prone to escalating rates of obesity. An extensive systematic review and meta-analysis conducted in 199 countries from 1980–2008 showed that the average rate of BMI increase per decade is 0.4 kg/m^2 in men and 0.5 kg/m^2 in women. The meta-analysis revealed concerning statistics specifically for South Africa, noting an increase in BMI at a rate of 2.9 kg/m^2 per decade for males and 1.6 kg/m^2 per decade for females during 2000–2008. Longitudinal data derived from other South African studies support these findings and corroborate an upward trend in obesity. In developing countries, the obesity problem is compounded by urbanization, a change in diet to low-cost, easily accessible, high sugar, carbohydrate-dense, and nutrient-deficient diets, allowing for little variety. Obese individuals from lower-income settings or areas where food insecurity prevails, are expected to have more profound micronutrient deficiencies. Although this study is the largest to date to investigate baseline micronutrient deficiencies before metabolic surgery in an African population, the limited number of deficiencies per income category did not allow us to perform reliable statistical analysis to assess the interplay between socio-economic and nutritional status.

Sun exposure and the presence of melanin play a significant role in the metabolism of 25(OH)D. Higher melanin concentrations have advantages for those who live in areas of intense sunlight exposure by reducing the harmful effects of ultraviolet light on the skin; however, it does reduce the efficacy of 25(OH)D metabolism. South Africa has a heterogeneous population with marked variation in skin concentration of melanin. Skin pigmentation and concentration of melanin is known to influence activation of vitamin D in the skin and varies amongst the different ethnic groups in South Africa. Globally, people of African descent with higher skin melanin content are known to be

predisposed to vitamin D deficiency and lower circulating 25(OH)D levels. 25(OH)D levels were thus assessed at baseline as noted and compared amongst the different ethnic groups included in the study cohort.

A recent systematic review and meta-analysis describing 25(OH)D deficiency in Africa, with high levels of sunlight, noted a pooled prevalence of low 25(OH)D status of 18.46%. Further, mean serum 25(OH)D levels were lower in South Africa compared to the rest of sub-Saharan Africa. This was attributed to lifestyle factors and increasing urbanization. The optimal serum 25(OH)D for skeletal health is controversial, and concentrations for extra skeletal health have not been established. The Institute of Medicine (IOM) favors maintaining the serum 25(OH)D between 50 and 100 nmol/L for bone health. The US National Osteoporosis Foundation, the International Osteoporosis Foundation [IOF] and the American Geriatric Society suggest that a minimum level of 75 nmol/L is necessary to minimize fracture risk. Musculoskeletal health and fracture risk is a concern in people who undergo metabolic surgery, and obesity is a predisposing factor for 25(OH)D deficiency, hence the rationale for adopting the higher threshold of 72.5 nmol/L in this study to denote sufficiency and to regard a circulating level of 25(OH)D ≤ 50nmol/L as deficient.

The prevalence of 25(OH)D deficiency was high (57%) in the relatively young cohort of these study participants (mean age 45 years; [37-51 years]). The highest percentage of 25(OH)D deficiency was documented in those of mixed ancestry/Asian decent (51/65; 78%) and in black Africans (4/6; 67%), a finding that supports the notion that melanin concentration does play a role in the skin activation of 25(OH)D. It is, however, noteworthy that the prevalence of 25(OH)D deficiency in the study participants was significantly higher than the figures reported for the general population in the region thereby implicating excess body weight, irrespective of skin melanin content, as a contributor to 25(OH)D deficiency.

The association between 25(OH)D and obesity has not been fully established, and various theories have been postulated. 25(OH)D metabolism hinges on sun exposure which may be reduced in obese individuals, who tend to partake in less outdoor physical activities. Furthermore, 25(OH)D may be sequestered in the adipose tissue of obese persons and, as such, has a reduced bioavailability. While the pathophysiology of 25(OH)D deficiency in obesity remains uncertain, the important role of 25(OH)D sufficiency to ensure optimal skeletal health are widely accepted. This study documented an inverse correlation between PTH and 25(OH)D. PTH secretion is expected to increase with a decrease in bioavailable 25(OH)D and a negative calcium balance. Chronic exposure of the skeleton to elevated circulating PTH is known to contribute to bone loss and decreased skeletal integrity. The findings argue for the critical interpretation of PTH to inform the routine monitoring and appropriate supplementation of 25(OH)D in obese patients, particularly those scheduled for metabolic surgery.

Most of the study participants (136/154) were women with a median age of 45 years (37–51) and the majority were either of mixed/Asian (65/154; 42%) or European (83/154; 54%) descent. Iron deficiency was noted in near half (46%) of the women in this study, with iron deficiency anemia present in 12%. A study by Phatlhane et al. in otherwise healthy non-pregnant South African adults (median age 30 years) documented iron deficiency in a concerning 56,6% of their female participants and iron deficiency anemia in 9.8%; findings in keeping with those described here. Diagnostic criteria employed to define iron deficiency and iron deficiency anemia were similar in this study. They attributed the presence of iron deficiency in their cohort to menstrual blood loss and limited intake of iron rich foods. In another local study, the association between obesity and iron deficiency in women aged 25-49 years in rural areas in the Free State Province of South Africa was explored. Iron-deficiency was noted in a far lower percentage of their participants (4.1%). Studies from elsewhere in the world looking at micronutrient status in the morbidly obese and prior to bariatric surgery document iron deficiency in a comparatively lower percentage of their cohorts (<10%). Detailed dietary assessment and interrogation of menstrual patterns was not performed in this study making it impossible to define causality of these findings or explain the discrepancy compared to other published data. The high prevalence of iron deficiency in the South African setting prior to metabolic surgery is important and noteworthy and should prompt assessment of iron status prior to performing metabolic surgery.

25(OH)D, folate, and iron deficiencies were more prevalent in participants with a BMI ≥45 kg/m^{2,} compared to those with a BMI <40kg/m^2, a finding also noted in other published studies. In fact, folate deficiency was exclusively seen in participants in the obesity class III or above. Interpretation of this data must, however, be done cautiously as only 11 study participants, representative of a minority of the cohort (7%) had a BMI <40 kg/m^2. Folate deficiency was observed in 18% of research participants, comparatively lower than other African studies, where folate deficiency was noted in 54% obese and non-obese women in Ghana. The Ghanaian study notes that folate deficiency may be particularly high in West Africa where folate-deficient diets are consumed. In the same

way, demonstrated low folate levels in 28% of non-pregnant women of childbearing age in Limpopo, South Africa. This study was performed 4 years after the introduction of mandatory food fortification with folic acid in South Africa. Additionally, low folate levels have been linked to poor socio-economic circumstances (SES), but limited numbers precluded an evaluation of the association between folate and SES in this study.

We did not quantify nutrient (including folate) intake in our study, but the South African National Food Consumption Survey- Fortification Baseline (NFCS-FB) in women of reproductive age, reassuringly indicated low rates of folate deficiency nationally. Interestingly at the time, 60% did not look for the food fortification logo on maize, bread, or flour products. Provincially, women and children in the Western Cape, Northern Cape, the Free State and Eastern Cape had significantly lower mean serum and red blood cell folate compared to other provinces. Still, the mean folate levels in the Western Cape where 58% of women were obese or overweight were sufficient. It is well established that overweight and obese individuals have lower serum folate concentrations than normal-weight individuals. Female folate deficiency is still noted during pregnancy and lactation despite food fortification due to increased metabolic needs. Globally the proposed contributing factors to folate deficiency in obese and overweight individuals include inflammation, insulin resistance and symbiosis in the microbiome. Additional considerations are increased urinary excretion, dilution of blood volume, and impaired folate absorption by the intestinal epithelium. We could not identify comparable South African cohorts to juxtapose our findings scientifically and did not evaluate the influence of these factors in our study.

Clinicians should maintain a high index of suspicion and a low threshold to test for micronutrient deficiencies in obese patients, especially those with a BMI ≥40 kg/m^2, irrespective of whether they are scheduled for metabolic surgery or not.

Evaluation of glycemic status was limited to determination of a fasting blood glucose and HbA1c and was available in 152 of study participants. Abnormal glucose homeostasis was present in a concerning number of participants (102/152; 67%). Of those 33/102 (32%) had newly diagnosed prediabetes and 13/102 (13%) unknown T2D thus representing 30% of this study cohort. Within obesity category III, 22% and 40% of women had prediabetes and T2D respectively, metabolic abnormalities not considered or required as inclusion criteria in this subgroup of the cohort. Optimal glycemic control was achieved in less than half of participants known with diabetes mellitus prior to study entry (42.8%). The high prevalence of undiagnosed prediabetes and T2D and the suboptimal control of known diabetes at baseline in subjects scheduled for bariatric surgery is noteworthy and must be addressed in clinical practice. It illustrates the significant number of unmet needs for T2D in sub-Saharan Africa. Evidence from the South African National Health and Nutrition Examination Survey (SANHANES-1 (2011–2012) indicated in people with T2D, 45.4% are unscreened and overall, that 80.6% of the T2D population had an unmet need for care. Obesity is one of the strongest risk factors for T2D and to limit the impact of this epidemic, urgent multilevel prevention and management actions are required.

This study has limitations. All participants were recruited from an existing pool of patients referred for metabolic surgery at a single tertiary hospital and extrapolation of the findings may thus not be applicable to the broader population. Findings in this study remain valuable as an initial step to uncover the baseline prevalence of micronutrient deficiencies in obese South Africans scheduled for metabolic surgery. With the projected increased prevalence of obesity on the African continent, the results caution for the judicial monitoring of patients considered for metabolic surgery as treatment method. Based on the data, it is recommended that a routine assessment of micronutrient status is performed; that as a minimum include the measurement of 25(OH)D, iron status and folate. Screening for T2D with an oral glucose tolerance test ± HbA1c determination and optimization of glycemic control in those known with T2D should be standard of care in obese individuals, including those scheduled for metabolic surgery.

CONCLUSION

In conclusion, the study documented micronutrient deficiencies and a concerning prevalence of abnormal glucose status in obese individuals scheduled Y for metabolic surgery. The appropriate detection and management of these nutritional deficiencies need to be moderated by the judicial use of resources and should include, at a minimum, the measurement of 25(OH)D and folate level and evaluation of iron status. Future efforts should seek to collate patient data on a national scale, to provide a more holistic, longitudinal picture of the relationship between obesity, metabolic surgery, and micronutrient status in the developing world, which may optimize evidence-based care.

ACKNOWLEDGEMENT

The Authors are thankful to the Management and Principal, Princeton College of Pharmacy, Narapally, Ghatkesar, Telangana, for extending support to carry out the research work. Finally, the authors express their gratitude to the Sura Pharma Labs, Dilsukhnagar, Hyderabad, for providing research equipment and facilities.

REFRENCES

1. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. Gastroenterology 2007;132:2087–102.
2. Douketis JD, Macie C, Thabane L, Williamson DF. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. Int J Obes 2005;29:1153–67.
3. Buchwald H, Williams SE. Bariatric surgery worldwide 2003. Obes Surg 2004;14:1157–64.
4. Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683–93
5. DeMaria EJ, Sugerman HJ, Meador JG, et al. High failure rate after laparoscopic adjustable silicone gastric banding for treatment of morbid obesity. Ann Surg 2001;233:809–18.
6. Suter M, Calmes JM, Paroz A, Giusti V. A 10-year experience with laparoscopic gastric banding for morbid obesity: high long-term complication and failure rates. Obes Surg 2006;16:829–35.
7. Suter M, Giusti V, Héraief E, Zysset F, Calmes JM. Laparoscopic Rouxen-Y gastric bypass: initial 2-year experience. Surg Endosc 2003;17: 603–9.
8. Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Luketich J. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg 2000;232:515–29.
9. Fisher BL, Barber AE. Gastric bypass procedures. Eur J Gastroenterol Hepatol 1999;11:93–7.
10. Alvarez-Leite JI. Nutrient deficiencies secondary to bariatric surgery. Curr Opin Clin Nutr Metab Care 2004;7:569–75.
11. Bloomberg RD, Fleishman A, Nalle JE, Herron DM, Kini S. Nutritional deficiencies following bariatric surgery: what have we learned? Obes Surg 2005;15:145–54.
12. 1. Kluetz PG, O'connor DJ, Soltys K. Incorporating the patient experi-ence into regulatory decision making in the USA, Europe, andCanada.Lancet Oncol.2018;19(5):e267–e274. doi:10.1016/S1470-2045(18)30097-4
13. US Department of Health and Human Services, Food and DrugAdministration, Center for Devices and Radiological Health, Centerfor Biologics Evaluation and Research.Guidance for Industry:Patient Preference Information–Voluntary Submission, Review inPremarket Approval Applications, Humanitarian Device ExemptionApplications, and De Novo Requests, and Inclusion in DecisionSummaries and Device Labeling;2016.
14. Postmus D, Mavris M, Hillege HL, et al. Incorporating patient pre-ferences into drug development and regulatory decision making:results from a quantitative pilot study with cancer patients, carers,and regulators.Clin Pharmacol Ther.2016;99(5):548–554. doi:10.1002/cpt.v99.5
15. healthcare Ifqaei. Background: what are patient preferences?Accessed 24 June,2019.5. UK R. NICE given grant to research patient preference;2016.Accessed 24 June, 2019.
16. Louviere JJ, Flynn TN, Carson RT. Discrete choice experiments arenot conjoint analysis.JChoiceModell.2010;3(3):57–72.doi:10.1016/S1755-5345(13)70014-9
17. Thurstone LL. A law of comparative judgment.Psychol Rev.1927;34(4):273–286. doi:10.1037/h0070288
18. Mangham LJ, Hanson K, McPake B. How to do (or not to do) . . .Designing a discrete choice experiment for application in a low-income country.Health Policy Plan.2009;24(2):151–158. doi:10.1093/heapol/czn047
19. Koledova E, Stoyanov G, Ovbude L, Davies PSW. Adherence andlong-term growth outcomes: results from the easypod.EndocrConnect.2018;7(8):914–923. doi:10.1530/EC-18-0172
20. Rosenfeld RG, Bakker B. Compliance and persistence in pediatricand adult patients receiving growth hormone therapy.Endocr Pract.2008;14(2):143–154. doi:10.4158/EP.14.2.143
21. Cutfield WS, Derraik JG, Gunn AJ, et al. Non-compliance withgrowth hormone treatment in children is common and impairs lineargrowth.PLoS One.2011;6(1):e16223. doi:10.1371/journal.pone.0016223
22. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC,Tynan A. Utilities and disutilities for attributes of injectable treat-ments for type 2 diabetes.Eur J Health Econ.2011;12(3):219–230.doi:10.1007/s10198-010-0224-8

23. Quitmann J, Bloemeke J, Silva N, et al. Quality of life ofshort-statured children born small for gestational age or idiopathicgrowth hormone deficiency within 1 year of growth hormonetreatment.Front Pediatr.2019;7:164. doi:10.3389/fped.2019.00164
24. Reed Johnson F, Lancsar E, Marshall D, et al. Constructing experi-mental designs for discrete-choice experiments: report of the ISPORconjoint analysis experimental design good research practices taskforce.Value Health.2013;16(1):3–13. doi:10.1016/j.jval.2012.08.2223
25. Maniatis AK, Thornton P, Hofman P, et al. The pivotal phase 3heiGHt Trial of Weekly TransCon™hGH vs. Daily hGH in treat-ment-naïve subjects with pediatric growth hormone deficiency. Posterpresented at the Pediatric Academic Societies/Pediatric EndocrineSociety Annual Meeting(PAS/PES), April 27-30, 2019 (BaltimoreMD).
26. Biospace. New Phase 2 data for somapacitan demonstrate its poten-tial as an efficacious once-weekly treatment for childhood growthhormone deficiency. Published Sept 282018.
27. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. Jama (2013) 309(1):71–82. doi: 10.1001/jama.2012.113905
28. Gao F, Zheng KI, Wang X-B, Sun Q-F, Pan K-H, Wang T-Y, et al. Obesity is a risk factor for greater COVID-19 severity. Diabetes Care (2020) 43(7):e72–4. doi: 10.2337/ dc20-0682
29. Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, et al. Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. Obes Rev (2020) 21(11):e13128. doi: 10.1111/obr.13128
30. Tamara A, Tahapary DL. Obesity as a predictor for a poor prognosis of COVID19: A systematic review. Diabetes Metab Syn (2020) 14(4):655–9. doi: 10.1016/ j.dsx.2020.05.020
31. Sowers JR. Obesity as a cardiovascular risk factor. Am J Med (2003) 115(8):37–41. doi: 10.1016/j.amjmed.2003.08.012
32. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the framingham experience. Arch Int Med (2002) 162(16):1867–72. doi: 10.1001/archinte.162.16.1867
33. James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. Obes Res (2001) 9(S11):228S–33S. doi: 10.1038/oby.2001.123
34. Caballero B. A nutrition paradox–underweight and obesity in developing countries. N Engl J Med (2005) 352(15):1514–6. doi: 10.1056/NEJMp048310
35. Astrup A, Bügel S. Overfed but undernourished: recognizing nutritional inadequacies/deficiencies in patients with overweight or obesity. Int J Obes (2019) 43 (2):219–32. doi: 10.1038/s41366-018-0143-9
36. Courcoulas AP, Yanovski SZ, Bonds D, Eggerman TL, Horlick M, Staten MA, et al. Long-term outcomes of bariatric surgery: a national institutes of health symposium. JAMA Surg (2014) 149(12):1323–9. doi: 10.1001/jamasurg.2014.2440
37. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric surgery versus intensive medical therapy for diabetes–5-year outcomes. N Engl J Med (2017) 376:641–51. doi: 10.1056/NEJMoa1600869
38. Sjöström L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, et al. Bariatric surgery and long-term cardiovascular events. Jama (2012) 307(1):56–65. doi: 10.1001/jama.2011.1914
39. Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB. Bariatric surgery and cardiovascular outcomes: a systematic review. Heart (2012) 98(24):1763–77. doi: 10.1136/heartjnl-2012-301778
40. Nguyen NT, Paya M, Stevens CM, Mavandadi S, Zainabadi K, Wilson SE. The relationship between hospital volume and outcome in bariatric surgery at academic medical centers. Ann Surg (2004) 240(4):586. doi: 10.1097/01.sla.0000140752.74893.24
41. Birkmeyer NJ, Dimick JB, Share D, Hawasli A, English WJ, Genaw J, et al. Hospital complication rates with bariatric surgery in Michigan. Jama (2010) 304 (4):435–42. doi: 10.1001/jama.2010.1034
42. Pories WJ. Bariatric surgery: risks and rewards. J Clin Endocrinol Metabol (2008) 93(11):s89–96. doi: 10.1210/jc.2008-1641
43. MacDonald KG, Long SD, Swanson MS, Brown BM, Morris P, Dohm GL, et al. The gastric bypass operation reduces the progression and mortality of non-insulindependent diabetes mellitus. J Gastrointest Surg (1997) 1(3):213–20. doi: 10.1016/ S1091-255X(97)80112-6
44. Krzizek EC, Brix JM, Herz CT, Kopp HP, Schernthaner GH, Schernthaner G, et al. Prevalence of micronutrient deficiency in patients with morbid obesity before bariatric surgery. Obes Surg (2018) 28(3):643–8. doi: 10.1007/s11695-017-2902-4

45. Flancbaum L, Belsley S, Drake V, Colarusso T, Tayler E. Preoperative nutritional status of patients undergoing roux-en-Y gastric bypass for morbid obesity. J Gastrointest Surg (2006) 10(7):1033–7. doi: 10.1016/j.gassur.2006.03.004
46. O'Kane M, Parretti HM, Pinkney J, Welbourn R, Hughes CA, Mok J, et al. British Obesity and metabolic surgery society guidelines on perioperative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery–2020 update. Obes Rev (2020) 21(11):e13087. doi: 10.1111/obr.13087
47. Parrott J, Frank L, Rabena R, Craggs-Dino L, Isom KA, Greiman L. American Society for metabolic and bariatric surgery integrated health nutritional guidelines for the surgical weight loss patient 2016 update: micronutrients. Surg Obes Relat Dis (2017) 13(5):727–41. doi: 10.1016/j.soard.2016.12.018
48. Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient–2013 update: cosponsored by American association of clinical endocrinologists, the obesity society, and American society for metabolic & bariatric surgery. Surg Obes Relat Dis (2013) 9(2):159–91. doi: 10.1016/j.soard.2012.12.010.
49. Kvaslerud AB, Hussain AI, Auensen A,Ueland T, Michelsen AE, Pettersen KI,et al. Prevalence and prognostic implication of iron deficiency and anaemia inpatients with severe aortic stenosis.Open Heart.2019;5:e000901.
50. Rheude T, Pellegrini C, Lessmann L,Wiebe J, Mayr NP, Michel J, et al.Prevalence and clinical impact of iron deficiency in patients with severe aor-tic stenosis referred for transcatheter aortic valve implantation.Am J Cardiol.2019;124:1442–8.
51. Hoes MF, Grote Beverborg N, Kijlstra JD, Kuipers J, Swinkels DW, GiepmansBNG, et al. Iron deficiency impairs contractility of human cardiomyocytes throughdecreased mitochondrial function.Eur J Heart Fail.2018;20:910–9.
52. Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS,et al.; IRON CORE Group. Iron deficiency across chronic inflammatory condi-tions: international expert opinion on definition, diagnosis, and management.AmJ Hematol.2017;92:1068–78.
53. Abdul-Jawad Altisent O, Puri R, Regueiro A, Chamandi C, Rodriguez-Gabella T,del Trigo M, et al. Predictors and association with clinical outcomes of the changesin exercise capacity after transcatheter aortic valve replacement.Circulation.2017;136:632–43.
54. De Larochellière H, Puri R, Eikelboom JW, Rodés-Cabau J. Blood disordersin patients undergoing transcatheter aortic valve replacement: a review.JACCCardiovasc Interv.2019;12:1–11.
55. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V,et al.; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failureand iron deficiencydagger.Eur Heart J.2015;36:657–68.