

# Flattening the biological age curve by improving metabolic health: to taurine or not to taurine, that's the question

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**ABSTRACT** The aging population is an important issue around the world especially in developed countries. Although medical advances have substantially extended life span, the same cannot be said for the duration of health span. We are seeing increasing numbers of elderly people who are frail and/or have multiple chronic conditions; all of these can affect the quality of life of the elderly population as well as increase the burden on the healthcare system. Aging is mechanistically related to common medical conditions such as diabetes mellitus, ischemic heart disease, cognitive decline, and frailty. A recently accepted concept termed 'Accelerated Biological Aging' can be diagnosed when a person's biological age—as measured by biomarkers of DNA methylation—is older than their corresponding chronological age. Taurine, a conditionally essential amino acid, has received much attention in the past few years. A substantial number of animal studies have provided a strong scientific foundation suggesting that this amino acid can improve cellular and metabolic health, including blood glucose control, so much that it has been labelled one of the 'longevity amino acids'. In this review article, we propose the rationale that an adequately powered randomized-controlled-trial (RCT) is needed to confirm whether taurine can meaningfully improve metabolic and microbiome health, and biological age. This trial should incorporate certain elements in order to provide the much-needed evidence to guide doctors, and also the community at large, to determine whether this promising and inexpensive amino acid is useful in improving human metabolic health.

Aging is a global health problem; and how to improve quality of life in the aging population is an important research paradigm.<sup>[1]</sup> Frailty and many chronic health conditions, such as diabetes mellitus and coronary artery disease, are well-recognized phenotypical features of aging. But these health issues can also occur in individuals who are not old chronologically, a circumstance that is sometimes called 'accelerated biological aging'.<sup>[2]</sup> Recent research suggested that frailty and many chronic health conditions are pathogenically linked to accelerated biological aging.<sup>[2]</sup> The precise patho-

genic mechanisms that lead to accelerated biological aging as well as many chronic health conditions are multiple, including increased rates of DNA methylation, spontaneous somatic mutations such as Clonal Hematopoiesis of Indeterminate Potential (CHIP), mitochondrial dysfunction and excessive endoplasmic reticulum stress.<sup>[3,4]</sup>

## BIOLOGICAL AGE AS THE UNDERLYING MODEL OF HEALTH PHENOTYPES

Recently, advanced computing capability including the use of artificial intelligence has allowed re-

searchers to identify biomarkers of DNA methylation to quantify the biological age of individuals. Furthermore, the phenotypical or biological age of a person has been shown to behave like a dynamic 'epigenetic clock' – which can be dialled forward with diseases and health events such as surgery, pregnancy, or COVID-19 infection.<sup>[5]</sup> Conversely, it can be reversed with certain interventions,<sup>[6]</sup> despite advancing chronological age that can only move forward. A phenotypical or biological age model, the Levine PhenoAge model, based on data input from nine commonly used blood tests was published in 2018 and it was subsequently validated to be predictive of 10-year survival, cognitive decline, and the onset of diabetes mellitus, after adjustment for an individual's chronological age, educational background, socioeconomic status and smoking habits, in a population that included those who were older than 80 years-old.<sup>[7-9]</sup> Furthermore, somatic mutations such as CHIP that have been shown to be strongly linked to an increased risk of cardiovascular disease, are also linked to age acceleration assessed by multiple biological age clocks, including the Levine PhenoAge model.<sup>[3]</sup> These findings suggest that epigenetic aging may be used to identify a population at high risk for adverse health outcomes, and as an important secondary outcome for phase II interventional trials.

Our recent work showed that biological age is also an important predictor of outcome in the acute care setting.<sup>[10,11]</sup> Biological age in excess of an individual's chronological age had a dose-dependent association with risk of hospital mortality and unplanned intensive care unit readmission, with and without adjusting for important covariates such as chronological age, comorbidities and severity of the acute illness. Taken together, these studies suggest that being biologically older (due to DNA methylation) than one's chronological age is associated with a lower physiological or biological reserve to cope with acute stressful events as well as a trajectory of accelerated aging, regardless of co-existing comorbidities.

## TRADITIONAL INTERVENTIONS TO IMPROVE HEALTH AND THEIR EFFECTS ON BIOLOGICAL AGE

Exercise is as an important lifestyle element that has been consistently shown to improve a wide ra-

nge of health outcomes including aging-related cognitive decline<sup>[12]</sup> and frailty.<sup>[13]</sup> Recent research showed that a combination of exercise with nutritional intervention can slow down biological aging within 4 weeks to 12 months in small human trials.<sup>[14-16]</sup> More important, in the secondary analysis of a factorial randomized-controlled-trial (RCT) assessing the effects of diet and diet-exercise in obese adults over a 12-month period, diet alone and diet with exercise decreased biological age measured by the Klemmera-Doubal Method more than both the exercise alone and the control groups (-2.4 and -2.2 vs. -0.2 and 0.2 years compared to their baseline on enrolment respectively,  $P < 0.05$  for the between group-differences).<sup>[16]</sup> A recent systematic review also showed that exercise may not offer additional benefits to a hypocaloric diet in adults who were overweight, or obese with type II diabetes mellitus.<sup>[17]</sup> The mean differences in change of body weight, body mass index, waist circumference, fat-free mass, fat mass, fasting glucose, glycated hemoglobin (HbA1c) or Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) were not significantly different between the combined exercise with hypocaloric diet and hypocaloric diet alone groups. These studies suggest that nutritional interventions are a key element in reducing biological age and improving health.

There is no doubt that adequate and balanced nutritional intake is essential to good health. The roles of macronutrients had been extensively studied, and the current World Health Organization guidelines suggest that caloric intake should be in balance with energy expenditure, and total intake of fats, saturated fats, free sugars, trans-fats should be less than 30%, 10%, 10%, and 1% of total energy intake, respectively. Recent scientific studies have started to explore and lead us to understand the importance of nutritional elements beyond macronutrients in prolonging healthy aging.<sup>[18]</sup>

## TAURINE AS AN EMERGING NUTRITIONAL INTERVENTION TO REPROGRAM BIOLOGICAL AGE AND HEALTH

Taurine (2-aminoethanesulfonic acid) has been traditionally considered as a conditionally essential amino acid in infants and children because defi-



ciency of taurine may hinder brain development.<sup>[19]</sup> Human milk contains taurine and formula milk is supplemented with taurine to compensate for insufficient endogenous taurine synthesis in infants and children. In adults, endogenous taurine synthesis occurs in discrete amounts, ranging from 0.4 to 1.0 mmol per day, depending on protein intake and hepatic function. The primary source of taurine for humans is the diet, especially seafood such as scallops, and dark meat, with an estimated daily intake that seldom exceeds 400 mg (3.2 mmol) for most people. The blood taurine levels have been shown to increase correspondingly with a higher dietary intake and oral supplementation. Taurine is not used by the body for protein synthesis and exists in higher concentrations in energy-demanding organs, such as the brain, retina, heart, pancreas and skeletal muscles, but its abundance almost invariably reduces as animals and humans age.<sup>[20]</sup> Interestingly, blood taurine levels can also be increased, at least temporarily, after a short period of exercise,<sup>[20]</sup> with some authors suggested that taurine may play a causal role in explaining why exercise is beneficial to human metabolic health by mediating atheroprotection.<sup>[21]</sup>

Each pancreatic  $\beta$ -cell produces more than 3000 insulin molecules per second.<sup>[22]</sup> Because pancreatic  $\beta$ -cells are a cornerstone of metabolic health and  $\beta$ -cell failure due to excessive endoplasmic reticulum (ER) stress is a major pathogenic step in the development of type II diabetes mellitus,<sup>[23]</sup> the effects of taurine on pancreatic  $\beta$ -cells and hence also metabolic health require further consideration. When administered as a supplement in animal studies, taurine has been reported to induce a variety of beneficial changes at a cellular level including optimizing mitochondrial function, reducing ER stress and transforming growth factor (TGF)- $\beta$  expression that can contribute to an increased pancreatic  $\beta$ -cell survival and/or trans-differentiation of  $\alpha$ -cells into  $\beta$ -cells.<sup>[24-27]</sup> At the organ function level, taurine has also been reported to improve bone,<sup>[20]</sup> retinal and brain health in animal studies,<sup>[28,29]</sup> and furthermore, in small human studies, improvements in glycemic control,<sup>[30]</sup> exercise endurance<sup>[31]</sup> and myocardial function<sup>[32]</sup> after taurine supplementation have been reported.

The mechanisms by which taurine may improve cellular and organ function or health in general are

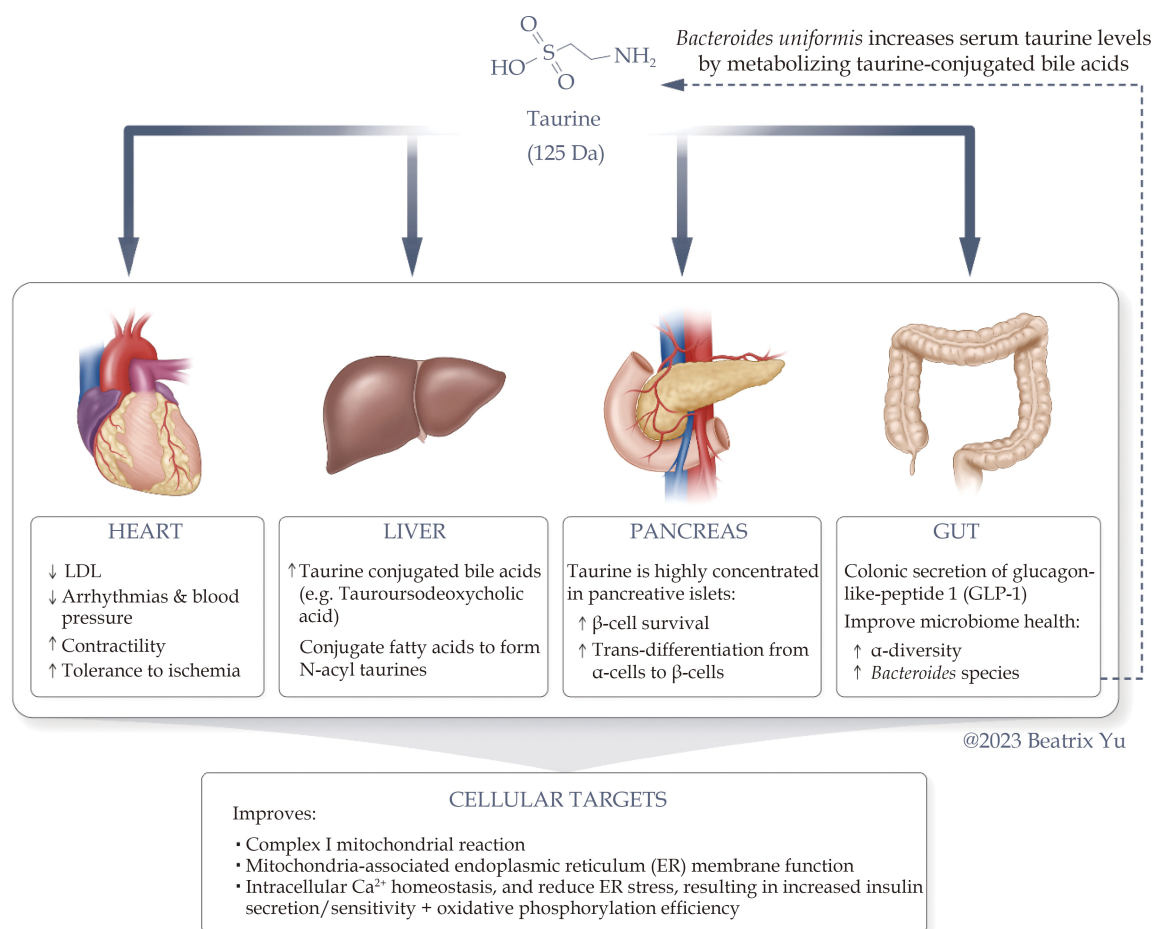
likely multiple, and not necessarily restricted to its direct actions. Specifically, some of the long-term benefits of taurine are believed to be mediated through its interactions with gut microbiome and bile acid conjugation,<sup>[33-35]</sup> both of which are currently believed to play a pivotal role in maintaining human health.<sup>[36]</sup> For instance, at least one of taurine's conjugated bile acids has been shown to stimulate colonic secretion of glucagon-like-peptide 1 (GLP-1) through activation of the Takeda-G protein-coupled-receptor 5.<sup>[37]</sup> Taurine is also needed to conjugate fatty acids to form N-acyl taurines in the liver,<sup>[38]</sup> which have been shown to mediate release of GLP-1.<sup>[39]</sup> The association between GLP-1 release and taurine supplementation has potential important clinical implications as the use of GLP-1 receptor agonists is now widely accepted as an effective metabolic therapy for patients with diabetes mellitus and people who are overweight.<sup>[40,41]</sup> Furthermore, both taurine and taurine-conjugated bile acids (e.g., tauroursodeoxycholic acid – TUDCA) may directly activate insulin receptors (IRs) by binding to docking sites not related to the insulin binding sites on the IRs,<sup>[42,43]</sup> thereby improving glucose homeostasis and the other cellular functions related to IRs, including IRs in the brain.<sup>[44]</sup> Calorie restriction (CR) has been consistently shown to improve metabolic health and longevity in a wide range of animal species and taurine acts biologically as a CR mimetic.<sup>[45]</sup> Mechanistically, CR could alter gut microbiome through which it would increase the intestinal levels of taurine and taurine-conjugated bile acids,<sup>[46]</sup> and transplantation of microbiota from mice with CR to *ad libitum* fed mice triggered CR-like changes in levels of taurine and taurine conjugates in the mucosa of the ileum.<sup>[47]</sup> Therefore, there is a strong scientific basis to support the hypothesis that taurine supplementation could improve long-term metabolic health, including optimizing blood glucose control and HbA1c levels, through multiple biologically plausible mechanisms. Because HbA1c has a dose-related positive relationship with long-term all-cause mortality, cardiovascular mortality, and cardiovascular events in both diabetic and non-diabetic individuals,<sup>[48,49]</sup> determining whether taurine can improve long-term plasma glucose control, as reflected by HbA1c, has considerable clinical importance.



Specific to the heart, taurine and TUDCA have also been shown to offer some benefits, including improvements in myocardial contractility and exercise capacity of cardiovascular testing,<sup>[32,50,51]</sup> tolerance to ischemia,<sup>[52]</sup> and a reduction in QT interval,<sup>[53]</sup> cardiac arrhythmias,<sup>[54,55]</sup> blood pressure,<sup>[56]</sup> trimethylamine N-oxide (TMAO) induced atherosclerosis,<sup>[57]</sup> and blood lipid levels including the low-density-lipoprotein (LDL) concentration in both individuals with and without diabetes mellitus.<sup>[58,59]</sup> Maintaining a long-term normal LDL level is associated with a decreased risk of coronary artery disease and stroke.<sup>[60,61]</sup> A large prospective multinational observational study had indeed showed that a high excretion of taurine in the urine (implying a high dietary intake of taurine) had significantly lower body mass index, systolic and diastolic blood pressure, total cholesterol, and atherogenic index (defined as total cholesterol / high-density-lipoprotein [HDL]-cholesterol in this study) than those who had a lower urinary

taurine excretion.<sup>[62]</sup> Similarly, a recent observational study in Chinese population showed that having a low plasma taurine level was associated with an increased risk of developing metabolic syndrome within 5 years.<sup>[63]</sup> Taken together, epidemiological data suggest that a low taurine intake may increase an individual's susceptibility to cardiovascular and metabolic diseases; and conversely, a high dietary taurine intake may play a pivotal role in maintaining both long-term cardiovascular and metabolic health.

In addition being important to metabolic and cardiovascular health, taurine may also play a role in improving neurological health either directly or indirectly.<sup>[28]</sup> Plasma HbA1c levels in non-diabetic individuals were found to have a positive association with anxiety and depression.<sup>[64]</sup> If suboptimal glycemic control is a contributing factor in the development of anxiety and depression, theoretically taurine could be useful if it could optimize the HbA1c



**Figure 1** Potential mechanisms of taurine in reprogramming metabolic health.



levels. A recent 7-T proton magnetic resonance spectroscopy imaging study also showed that brain taurine concentrations were reduced among depressed young individuals compared to healthy controls,<sup>[65]</sup> suggesting that taurine may also play an unrecognized direct role in optimizing mental health in humans similar to what being demonstrated in animal studies.<sup>[66,67]</sup> Currently known pathogenic mechanisms potentially underlying the effects of taurine in reprogramming cardiovascular and metabolic health are summarized in Figure 1.

## WHAT ARE THE CRITICAL KNOWLEDGE GAPS ABOUT TAURINE AS A NUTRITIONAL INTERVENTION?

A recent multinational collaborative study published in *Science* systemically assessed the potential health benefits of taurine,<sup>[20]</sup> and found that a reversal of the decline in blood taurine levels through taurine supplementation, at a pharmacological dose of equivalent to 3 g/day for an average adult human, increased the health span and life span in middle-aged mice by 10%-12%, and health span (including a lower fat mass, better bone density, reduced fasting glucose by 19%, and reduced markers of mitochondrial and DNA damage) in older nonhuman primates (at age equivalent to 45-year old humans) compared to control animals without taurine supplementation. They concluded that the missing piece to confirm the clinical utility of taurine as an efficacious therapeutic agent to minimize aging-related health problems in humans now is a well-controlled and adequately powered RCT.

Before the publication of this taurine animal study,<sup>[20]</sup> the results of a small number of human clinical trials assessing the effects of taurine, in particular its benefits on metabolic health such as glycemic control, were summarized.<sup>[30]</sup> Although the pooled results of this meta-analysis showed that HbA1c concentrations were reduced by 0.4% with taurine supplementation, its validity is limited by the small number of patients included ( $n = 209$  from five trials), and the short duration of taurine supplementation ( $< 16$  weeks). Most importantly, the largest included trial ( $n = 63$ ) had a high-risk of bias in random-sequence generation and allocation concealment. One more RCT ( $n = 120$ ) assessing taurine in

patients with diabetes mellitus has been published since the publication of this meta-analysis; and it reported that taurine supplementation (1 g/day) for 8 weeks resulted in lower serum insulin levels and improved HOMA-IR, as well as reduced biomarkers of endothelial dysfunction. HbA1c was not significantly different between the placebo and taurine groups in this most recent RCT, a finding likely related to the short duration of the intervention relative to the long half-life of erythrocytes and HbA1c.<sup>[68]</sup> It has been shown that about 50% of an HbA1c value represents an individual's glucose exposure in the preceding 30 days, 40% represents exposure in the previous 31 to 90 days and the remaining 10% in the previous 91 to 120 days.

In summary, improving the health span to match the already extended life span of the aging population in many developed countries is of paramount importance. There is a substantial mismatch between the strong scientific foundation supportive of the health benefits of taurine in animal studies and the quality of clinical trials assessing the efficacy of taurine in human health. Recent advances have allowed us to move beyond targeting the traditional markers of health such as blood pressure, blood lipid and glucose levels, to be able to quantify one's biological age, and changes over time, by utilising objective blood biomarkers. Emerging evidence now suggests that taurine, which has been labelled as a potential longevity amino acid,<sup>[18]</sup> may play a complementary yet currently unquantified role in providing health benefits beyond those of a standard balanced diet as part of healthy human aging. Taurine is currently synthesized commercially in a pure form (hence also suitable for vegan consumption), and the cost is low ( $< \text{US\$1}$  per 1g).<sup>[69]</sup> Significant side effects and drug interactions in association with the use of taurine have not been reported, although currently its use in the community is not widespread. There is an urgent need to move forward to identify innovative ways to prevent accelerated biological aging, ultimately improving human health span (and not just life span), both for individuals, and to reduce the aging-related healthcare burden to the society. An adequately powered RCT, specifically to assess the effectiveness of taurine in human health is increasingly justified to support the concerted effort to tackle this challenge.



## THE KEY ELEMENTS REQUIRED OF A RCT TO ASSESS THE METABOLIC HEALTH BENEFITS OF TAURINE

In response to the scientific observations generated by the recent landmark taurine study in animals,<sup>[20]</sup> a carefully designed trial is justified to confirm the health benefits of taurine in humans. Positive RCT results, indicating the ability of supplemental taurine to improve aspects of human health, would have enormous potential to improve current medical practice and the quality of life of the general population, especially elderly citizens, who appear to be a high-risk group for relative taurine deficiency. We will describe the desirable elements of a RCT in studying the benefits of taurine in humans using the Population, Intervention, Comparator, Outcome, and Time frame (PICOT) format.<sup>[70]</sup>

### Population

It remains uncertain whether the benefits of taurine on glucose metabolism and biological age are consistent across the range of chronological age, and underlying pre-existing co-morbidities, particularly diabetes mellitus status (or genetic predisposition to develop diabetes mellitus) of the individual. Plasma taurine levels are lower in patients with diabetes mellitus compared to healthy controls,<sup>[71,72]</sup> and a large human observational study showed that blood taurine levels might differentially modulate the effects of diabetes-related genes on improvement of insulin sensitivity among overweight/obese patients on weight-loss diets.<sup>[73]</sup> As such, it is important that the study population for a RCT be stratified according to these important covariates (e.g., older than 45 years-old vs. younger than 45 years-old, diabetes mellitus vs. without diabetes mellitus) and with their potential interactions with taurine's effectiveness assessed statistically.<sup>[74]</sup> Because plasma taurine levels are normally regulated by the kidneys,<sup>[72]</sup> and excessive accumulation of taurine has been reported in patients requiring long-term dialysis,<sup>[75]</sup> participants who have advanced renal failure should be excluded from such RCT. Similarly, patients who have a significant clinical bleeding disorder (e.g., immune thrombocytopenic purpura with a platelet count  $< 100 \times 10^9/L$  or those treated with dual antiplatelet agents) should likely be excluded because

taurine has been shown to exert mild in vitro antiplatelet activity in one study.<sup>[76]</sup>

### Intervention

Existing evidence suggests that taurine supplementation at a dose well above the standard daily dietary intake level ( $< 400$  mg) may improve glucose and lipid metabolism. Taurine is relatively non-toxic, even in relatively large doses (up to 6 g per day),<sup>[76,77]</sup> and the interventional dose recommendation should be large enough to ensure that any negative result is not the consequence of insufficient dosing. The recent taurine trial on nonhuman primates used an equivalent dose that was between 3 and 6 g per day for an 80-kg person and this could represent a reasonable dose range for any human RCTs.<sup>[20,78]</sup>

### Comparator

The study should be randomized by a suitably concealed method, and double-blind using an indistinguishable placebo so that in addition to removing investigator bias, participants' health behaviors will not confound the beneficial effects (or a lack thereof) of the study intervention.

### Outcomes

Using long-term survival as a primary outcome is desirable but difficult; any demonstrable difference in this outcome will require a substantial sample size with prolonged follow-up (e.g., 5 years or longer) if the effect size is relatively small (or modest at best). Realistically, a number of robust surrogate outcomes should be evaluated in a well-controlled RCT before powering a RCT using lifespan as an outcome. For instance, a reduction in HbA1c is desirable especially for diabetic patients.<sup>[48,49]</sup> As noted previously, most published human trials were underpowered,<sup>[30]</sup> without considering the importance of the variability in HbA1c,<sup>[79]</sup> and with an inadequate study duration and follow-up to allow for the substantially long half-life of HbA1c. Biological age based on DNA methylation biomarkers according to the Levine PhenoAge or newer biological age models is increasingly being recognized as an important dynamic health parameter,<sup>[8-11]</sup> and hence it can also be used as a surrogate outcome in assessing the benefits of taurine supplementation. Other biomarkers with important clinical correlates



should also be considered as secondary outcome variables. For example, because LDL concentration is a strong predictor of cardiovascular events such as stroke,<sup>[60,61]</sup> it would be useful to evaluate whether taurine may improve LDL concentrations in humans. Ideally, a RCT should assess the health benefits of taurine in a comprehensive way, including functional end-points such as improved exercise tolerance<sup>[31]</sup> and mood or mental health,<sup>[63–65]</sup> using 6-min walk test and reliable and valid self-reporting questionnaires, respectively.<sup>[80–83]</sup>

Finally, it is desirable to confirm the mechanistic reasons through which taurine may mediate its benefits. In this regard, it will be interesting to assess the effects of taurine on gut microbiome (including alpha-diversity and *Akkermansia muciniphila* and *Bacteroides uniformis*) and to determine whether it is taurine, taurine-conjugated bile acids or both that are important in improving health.<sup>[33–35,46,47,84,85]</sup> The relative effects of taurine and taurine-conjugated bile acids on any positive health outcomes will, however, require formal interaction and mediation analyses as described in our earlier discussion.<sup>[74]</sup>

### Time Frame

In order to demonstrate the potential metabolic health benefits of taurine, a RCT with follow-up longer than a few weeks is needed. The current evidence indicates that nonhuman primates are an indispensable resource for evaluating the efficacy

and safety of novel therapeutic strategies targeting clinically important metabolic diseases, including dyslipidemia and diabetes mellitus.<sup>[86]</sup> We believe that a 6-month or longer interventional period matching what was successfully done on nonhuman primates will be an acceptable time frame in assessing potential efficacy of taurine on human metabolic health in a RCT.<sup>[20]</sup> A 6-month interventional period would also be considered adequate in capturing taurine's potential effects on HbA1c and LDL. The desirable features of a RCT assessing the health benefits of taurine are summarized in Table 1.

### CONCLUSIONS

Deteriorating metabolic health is one of the major phenotypical expressions of biological aging. A well designed and adequately powered human RCT assessing the health benefits of taurine will help to establish whether oral daily taurine supplementation can improve metabolic health including HbA1c and blood lipid levels, biological age of a person, mental health feeling, and daily physical activity ability. Positive findings from this study will change clinical practice as we are facing an aging population with increasing medical conditions such as diabetes mellitus, frailty, and cognitive decline. Furthermore, any synchronized improvements in metabolic health parameters and biological age of the participants will confirm the clinical utility of using biological age as

**Table 1** Desirable features of a randomized-controlled-trial (RCT) in assessing the metabolic health benefits of taurine in humans.

| Trial characteristics                                                                          | Desirable features                                                                                                                                                                                                                                                                                 |
|------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Blinding                                                                                       | Double blinded with indistinguishable placebo.                                                                                                                                                                                                                                                     |
| Allocation concealment                                                                         | Variable block lengths.                                                                                                                                                                                                                                                                            |
| Parallel vs cross over                                                                         | Parallel design.                                                                                                                                                                                                                                                                                   |
| Follow-up duration                                                                             | Longer than the lifespan of erythrocytes if glycated hemoglobin (HbA1c) is used as the primary outcome, or at least 6 months similar to the recent nonhuman primate study [20,86].                                                                                                                 |
| Testing interactions between study intervention and participants' major health characteristics | Stratified randomization with formal statistical analysis of the interactions for taurine's effectiveness on metabolic health between older and younger patients, or between those with and without diabetes mellitus [74].                                                                        |
| Sample size                                                                                    | Allowing for lost to follow-up and a large variability in HbA1c (if this is used as the primary outcome) [79].                                                                                                                                                                                     |
| Intervention                                                                                   | Adequate dose given daily oral taurine intake up to 6 grams per days is considered safe to exclude a false negative trial from inadequate dosing [28,76,77].                                                                                                                                       |
| Data analysis                                                                                  | Bonferroni adjustment for secondary outcomes (if there are more than one)                                                                                                                                                                                                                          |
| Outcomes                                                                                       | Including patient-centered functional outcomes [80–83] and mechanistic outcomes such as microbiome health and plasma taurine and taurine-conjugated bile acid levels [33–35,84,85] (which will confirm study drug compliance and also adequate separation of the intervention and control groups). |



a health parameter and outcome in testing other health interventions. Currently WHO and many other professional nutritional guidelines have largely focused on macronutrients. If taurine is proven to be able to have the health benefits reported in the animal studies, this inexpensive amino acid will have a huge potential positive impact on healthcare resources utilization in addition to improving the quality of life for many of us.

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## Conflict of Interest Statement

None of the authors has any financial or non-financial conflict of interest to declare in relation to the subject matter or drugs discussed in this manuscript.

## AI Assistance in Writing

No artificial intelligence programs were used in the writing of any parts of this manuscript.

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