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Review

The role of thiamine dependent enzymes in obesity and obesity related chronic disease states: A systematic review

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SUMMARY

The WHO 2016 report indicates that worldwide obesity is rising, with over 600 million people in the obese range (BMI>30). The recommended daily calorie intake for adults is 2000 kcal and 2500 kcal for women and men respectively. The average American consumes 3770 kcal/day and the average person in the UK consumes 3400 kcal/day. With such increased caloric intake, there is an increased load on metabolic pathways, in particular glucose metabolism. Such metabolism requires micronutrients as enzyme co-factors. The recommended daily allowance (RDA) for thiamine is 1.3 mg/day and 0.5 mg thiamine is required to process 1000 kilocalories (kcal). Therefore, despite the appearance of being overfed, there is now increasing evidence that the obese population may nutritionally depleted of essential micronutrients. Thiamine deficiency has been reported to be in the region of 16–47% among patients undergoing bariatric surgery for obesity. Thiamine, in turn, requires magnesium to be in its active form thiamine diphosphate, (TDP). TDP also requires magnesium to achieve activation of TDP dependent enzymes, including transketolase (TK), pyruvate dehydrogenase (PDH) and alpha-keto glutaric acid dehydrogenase (AKGDH), during metabolism of glucose. Thiamine and magnesium therefore play a critical role in glucose metabolism and their deficiency may result in the accumulation of anaerobic metabolites including lactate due to a mismatch between caloric burden and function of thiamine dependent enzymes. It may therefore be postulated that thiamine and magnesium deficiency are under-recognized in obesity and may be important in the progress of obesity and obesity related chronic disease states. The aim of the present systematic review was to examine the role of thiamine dependent enzymes in obesity and obesity related chronic disease states.

1. Introduction

In 2008 it was estimated that 1·46 billion adults worldwide were overweight and 502 million people were estimated to be in the obese range [1]. The WHO 2016 report indicates that these figures have significantly increased, estimating more than 1.9 billion adults are overweight (BMI>25), of which over 600 million of these are obese (BMI>30) [2]. Alarmingly, childhood obesity levels have risen in tandem with adult obesity. WHO statistics reveal that 41 million children under the age of 5 were overweight or obese in 2014 [2].

Increasing obesity is primarily due to increased consumption of calories [3,4]. The recommended daily calorie intake is 2000 kcal and 2500 kcal for adult women and men respectively [4]. The average American consumes 3770 kcal/day and the average person in the UK consumes 3400 kcal/day [1]. These figures are steadily rising due to the ready availability of 'high sugar, low nutrient' foods, that characterize the North American and Western European diet [5]. Chronic calorie excess is now endemic in Western society, with a reported 35–40% North Americans having BMI's in the obese range (BMI>30) [4]. Indeed, obesity has now overtaken smoking to become the number one cause of preventable death in some of the Western nations [6–8].

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The burden of obesity worldwide now poses a significant risk to population health and some experts warn that the obesity pandemic threatens to reverse the gains achieved in risk reduction for cardiovascular and cancer deaths over the past three decades [1,4,9]. The caloric burden on individuals in Western societies has increased as a consequence of changing diet. This has imposed a sugar rich nutritional intake on a metabolism evolved in a sugar poor evolutionary environment [10–13]. Total health-care costs attributable to obesity and overweight are projected to double every decade to account for 16–18% of total US health-care expenditure by 2030 [1].

Despite the appearance of being overfed, there is now increasing evidence that this population is nutritionally depleted of essential micronutrients and vitamins [14–16]. In 2012 the National Research Council reported that >80% Americans consumed a diet, which was deficient for vitamins and minerals [15,17]. The NHANES 3 study reported that multi-nutrient deficiencies were more prevalent in those with a BMI in the obese range than in the normal population [18–21]. In the present review we will examine the role of thiamine, an essential component in the metabolism of glucose, in patients with obesity.

1.1. Search strategy and methodology

This review set out to examine, in a systematic manner, studies that report association between obesity, thiamine and/or magnesium deficiency, and proposes the novel concepts that a combined deficiency of thiamine and magnesium may result in loss of responsiveness to insulin by the pyruvate dehydrogenase enzyme complex, and that this may serve as the metabolic fulcrum underpinning pseudohypoxic disease processes.

A PubMed literature search was performed in accordance with the PRISMA statement. The search focused on obesity and bariatric surgery in relation to thiamine or magnesium deficiency. Search keywords included: “bariatric surgery” OR “obesity” OR “non-insulin dependent diabetes” OR “type 2 diabetes” OR “metabolic syndrome” AND “thiamine” OR “thiamine deficiency”, AND “magnesium” OR “magnesium deficiency”. Inclusion criteria for each article were: an experimental or observational measurement of thiamine and or magnesium in relation to obesity or bariatric surgery at any age in human participants, between 1946 and October 2017 (see appendix 1). Additional papers, which were found through bibliographic reviews, were also included (see appendix 2).

Databases including MEDLINE, science direct, Scopus, Google scholar and Cochrane were searched from inception to October 2017. Observational studies were reviewed using the MOOSE checklist for guidance.

Citations from searches were imported into referencing software Endnote X7, whereupon title and abstract were screened for inclusion criteria [22]. Case studies, case reports and animal studies were excluded. Supporting evidence was provided by *in vitro* and *ex vivo* cellular studies of adipocytes in eligible human studies. There were no language or date restrictions. A copy of articles that met the inclusion criteria was obtained for full-text review. No article was unavailable.

1.2. Thiamine metabolism

Thiamine (Vitamin B1) is a water-soluble vitamin, that is required for the metabolism of glucose [23]. Thiamine is commonly found in meat (particularly pork), eggs, fish and whole grains [23]. Indeed, legislation in the United States and Australia requires that certain staple foods, such as bread, be fortified with thiamine [24]. Many ‘breakfast cereal’ type foods are also supplemented [25,26], and ‘over the counter’ thiamine containing multivitamins are now widely available [27].

Under normal physiological and nutritional conditions, the average adult human has approximately a 3-week reserve of thiamine in the liver. It is postulated that these reserves become rapidly depleted in disease, surgery or times of sustained physiological stress [28–33].

The measurement of thiamine in red blood cells is known to reflect nutritional status, and is not perturbed by the systemic inflammatory response [34–36]. Therefore, it is of interest that thiamine deficiency has been reported to be in the region of 16–29% among patients undergoing bariatric surgery for obesity [37–39], and this deficiency was reported to be even higher (31–47%) among some ethnic groups [15,38]. These findings are endorsed by a cross-sectional study of thiamine consumption in a population of 1,100 Mexican-American children, generated from NHANES data, which reported that thiamine consumption may be inversely associated with obesity in that group [40].

Thiamine deficiency has also been reported to be present in up to 75% of both type 1 and type 2 diabetics [41], and urinary excretion of thiamine has been reported to be 24 times higher in Type 1 diabetes and 16 times higher in type 2 diabetes as compared to normal controls [41]. Hence, thiamine deficiency has been proposed as a mediator of insulin resistance and loss of oxidative resilience in diabetes [42].

A pilot cross-over prospective randomized controlled trail (PRCT) ($n = 12$) reported that thiamine supplementation (100 mg taken three times per day for 6 weeks) resulted in significant decrease in 2-h plasma glucose relative to baseline (8.78+/-2.20 vs. 9.89+/-2.50 mmol/L, $p = 0.004$) [43]. It has also been reported that thiamine supplementation may exert a nephro-protective effect in NIDDM patients with evidence of early stage diabetic nephropathy and pilot studies have yielded encouraging results [44,45].

Given that the recommended daily allowance for thiamine is 1.3 mg/day, and that the average daily intake of thiamine from food for American adults is 1.87 mg and 1.39 mg in men and women respectively [46], and from the combination of food and supplements is 4.90 in both men and women [47], it is perhaps surprising that there are reported deficiencies in the obese. However, the current recommended daily allowance for thiamine is based on studies undertaken in the 1930's on healthy volunteers [48]. At this time daily calorie intakes were far lower than today. Nevertheless, from this work it may be assumed that 0.5 mg thiamine is required to process 1000 kcal (kcal) [18,23,49]. On the basis of a 4000 kcal/day intake, it might be expected that an appropriate RDA would be 2.0 mg/day. However, this would assume a linear relationship between calories consumed and thiamine requirement.

1.3. Pre-bariatric surgery related evidence of thiamine deficiency

A comprehensive literature search reveals 53 case reports describing the development of Wernicke's encephalopathy in patients during the post-operative period following bariatric surgery. It is therefore surprising that there are only five studies published that sought to quantify the extent of pre-operative thiamine deficiency in patients undergoing bariatric surgery [37–39,50,51]. Nath et al. report a 16.5% prevalence of preoperative thiamine deficiency [39]. Carrodeguas et al. and Flancbaum report a prevalence of 15.5% and 29% low thiamine concentrations in obese patients prior to bariatric surgery respectively [37,38]. Peterson et al. also report significant thiamine deficiency in patients prior to bariatric surgery, and note a significant racial disparity (patients of Hispanic origin = 33%), which is in keeping with the ethnic preponderance reported by Flancbaum et al.