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

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Abstract

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 1.3mg/day and 0.5mg 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.
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).

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
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.
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.

**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 trial (PRCT) (n= 12) reported that thiamine supplementation (100mg 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 1.3mg/day, and that the average daily intake of thiamine from food for American adults is 1.87mg and 1.39mg 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 0.5mg thiamine is required to process 1000kcal (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.

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 (38, 50). Aron-Wisnewsky et al report a preoperative prevalence of thiamine deficiency among 23% of the 22 women who underwent weight reduction surgery at their center (51).

However, it is worth noting that both Aron-Wisnewsky et al and Flancbaum et al reported their results based on measurement of serum thiamine concentrations (38). The National Institute of Health guidance on the...
measurement of thiamine status states that 'Levels of thiamine in the plasma are not reliable indicators of thiamine status' (52). Erythrocyte transketolase activity (ETKA) ratios, or erythrocyte (red cell) thiamine diphosphate (TDP) concentration measured in whole blood, are considered the gold standards for thiamine status, as they are based on the intracellular concentration of the vitamin (52).

Red cell TDP measurement from whole blood is recognized as a reliable measure of thiamine status, which some regard as equivalent or superior to ETKA measurement (53, 54). Red cell TDP assay may have an advantage over the ETKA assay for detecting tissue thiamine accumulation, however ETKA has the benefit of being a functional marker of thiamine status (55). Red cell TDP is more commonly measured, as ETKA is a more time consuming assay to perform (56). In particular, processing of blood samples for ETKA assay is time and temperature dependent, as processing or storage delay renders the sample prone to variable kinetics (57). Talwar and colleagues have reported that direct measurement of whole-blood TDP mass is most accurately expressed when placed in the context of haemoglobin mass (expressed in units: nanogram of TDP per gram of haemoglobin i.e. ng/g Hb) (54) as this corrects for unavoidable pipetting related volume sampling error.

Red cell TDP measurement was used in two of the bariatric surgery studies described above (37, 39). It is interesting to note however that the normal ranges and deficiency thresholds listed for each study vary significantly between institutions, and that certain patients deemed to be deficient in one study would not have met the criteria for biochemical deficiency in another (see
appendix 3) (37, 38, 58). Indeed, one of the studies provided no specific values of whole blood thiamine concentrations, however this study does correlate clinical criteria of symptoms related to thiamine deficiency with biochemically proven deficiency measured in whole blood (i.e. red cell thiamine diphosphate) (38).

Overall, there is some evidence of an association between thiamine deficiency and obesity, however given the scale of the problem there is a relative paucity of robust data available describing thiamine status in obese patients. This is surprising for a patient group who are known to be at risk of manifesting clinical signs of thiamine deficiency in the postoperative period after undergoing bariatric surgery (51, 59-63).

The role of thiamine in glucose metabolism

In the obese patient, most calories are in the form of glucose and there are several key enzymes that require thiamine as a co-factor (64-66). Briefly, a glucose load causes the pancreas to secrete insulin (67). Insulin causes the expression of GLUT receptor transporters on the membrane of non-endothelial and non-mesenchymal cells (68, 69). Glucose is taken into the cell where it is metabolized to pyruvate via the glycolytic pathway (70, 71). Under ideal conditions pyruvate enters the mitochondrialion and is converted to Acetyl-CoA through the action of pyruvate dehydrogenase (PDH) (64). Acetyl-CoA combines with oxaloacetate to form citrate and thence through the action of alpha ketoglutaric acid dehydrogenase (KGDH), generates ATP via the (Kreb's) Tricarboxylic Acid (TCA) cycle (64). This may be considered to be the optimal metabolism of glucose i.e. ‘a clean burn’.
Thiamine in the form of thiamine diphosphate (TDP) (also known as thiamine pyrophosphate) is required as a co-factor for pyruvate dehydrogenase (PDH) and alpha ketoglutaric acid dehydrogenase (KGDH), both key enzymes for the TCA cycle. Therefore, thiamine deficiency compromises these enzymes and results in an altered metabolism of glucose.
Figure 1(a) Normal glucose metabolism in the presence of normoxia and adequate micronutrient concentration i.e. 'a clean burn'
Thiamine deficiency compromises PDH activity, hence pyruvate is unable to gain access into the mitochondrion for conversion to acetyl-CoA and thereby onto the TCA cycle (64). The resulting ‘glut’ of pyruvate in the cytosol triggers up-regulation of lactate dehydrogenase (LDH) activity (72). LDH mediates the increased production of lactate, which accumulates in the cytosol (73). This may be considered to be the suboptimal metabolism of glucose i.e. ‘a dirty burn’.
Figure 1(b) Altered glucose metabolism due to compromised TDP dependent enzyme function i.e. ‘a dirty burn’
Pentose Phosphate Pathway, lactic acid and fatty acid synthesis

The Pentose Phosphate Pathway (PPP) is a cytoplasmic pathway composed of two arms: one irreversible and the other reversible. The irreversible arm is oxidative and generates NADPH that plays a vital role in maintaining the cellular redox balance. NADPH provides essential redox potential for synthetic pathways e.g. fatty acid synthesis. The reversible arm is non-oxidative and links the products of the irreversible arm back into the glycolytic pathway (74).

The ‘glut’ of pyruvate generated by suboptimal PDH activity may cause diversion of glucose metabolism into the oxidative arm of the PPP (74, 75). This increased flux through the oxidative arm of the PPP may then generate a net excess of NADPH (75, 76). Interestingly, the conversion of pyruvate to lactate by LDH also requires the conversion of NADPH to NADP+, and excess of NADPH may therefore drive the reaction towards increased production of lactate (72, 77).

Furthermore, fatty acid synthesis requires the conversion of NADPH to NADP+; hence excess NADPH may also facilitate increased fatty acid synthesis (76, 78).

The significance of a sustained elevation of serum lactate concentration is well recognized as a marker of compromised oxidative resilience in the acute setting, and as such has an established prognostic value. The threshold of normality for blood lactate concentration is < 2.0 mmol/L. A recent publication by Varis et al highlights the finding that a concentration >2 mmol/L among patients admitted to an Intensive Care Unit (ICU) is consistently associated with a higher 90-day mortality than a lactate concentration ≤2 mmol/L (43% vs. 22%) (79).

Furthermore, patients who continue to manifest hyperlactatemia (>2 mmol/L) at ≥72 hours post admission to ICU are reported to have more than double the 90-
day mortality when compared with those patients whose lactate concentration has resolved to ≤2.0 mmol/L at the same time point (52% vs. 24%) (79). Chronic low-grade elevation of serum lactate concentrations at the upper limit of normal may therefore indicate a reduced oxidative reserve and an increased vulnerability to systemic insult and oxidative stress. Pepper et al conducted a systematic review and meta analysis of the correlation between mortality and elevated BMI among patients admitted to ICU (80). This highlighted the counter-intuitive perspective of the ‘obesity survival paradox’ by revealing that a BMI in the over-weight and obese ranges (BMI= 25 – 30 and 30 - 35 kg/m²) may be a protective factor for patients admitted to ICU with a diagnosis of sepsis, while a BMI in the morbidly obese range (BMI > 35 kg/m²) does not reduce mortality (80). However, this meta-analysis was contradicted by a more recent and larger meta-analysis conducted by Wang et al, which found that overweight, but not obesity or morbid obesity, was associated with lower mortality in patients admitted to ICU with a diagnosis of sepsis (80).

The implications of the thiamine deficiency state also extend directly to the non-oxidative reversible arm of the PPP. Transketolase (TK) is also a TDP dependent enzyme, which catalyzes the reversible arm of the PPP (81). Indeed, it is this enzyme which has shown promise for combined co-factor supplementation with magnesium (82). Compromised TK activity results in the accumulation of a precursor to nucleotide synthesis, ribose-5- phosphate (83). Indeed, accumulation of ribose-5-phosphate may serve to drive the process of cell division.
Genetic variation in thiamine transporters and thiamine dependent enzymes

SLC19-A2 and SLC19-A3 code for thiamine transporters 1 and 2 (ThTr1 and ThTr2) respectively (84-86). Genetic polymorphisms that compromise the integrity of ThTr1 and ThTr2 cause reduced active transport of thiamine across the enterocyte brush border and in the nephron, resulting in impaired thiamine absorption and increased renal loss. However, as passive absorption of thiamine also occurs, these defects have been successfully treated with thiamine supplementation (86).

Thiamine responsive megaloblastic anaemia (TRMA) occurs with ThTr1 defect (84, 86) and thiamine metabolism dysfunction syndrome-2 occurs with THTR-2 defect (85). TRMA patients develop non-type I diabetes mellitus and treatment with thiamine has been reported to delay the onset of diabetes (86, 87).

Similarly, defects of the genes that code for elements of the PDHC result in inborn errors of metabolism e.g. Leigh syndrome, which are also characterized by impaired glucose metabolism and increased lactic acid production (77, 88).

Due to the reliance of the nervous system upon carbohydrate metabolism, these syndromes may manifest profound neurological symptoms, such as developmental delay and ataxia (84, 88).

These conditions vary in severity and responsiveness to thiamine therapy according to the degree of penetrance of the genetic defect (77, 86). While these genetic variants provide valuable insight into thiamine dependent metabolic processes, the overall incidence of these conditions is very rare. For example,
Patel et al reviewed the literature published between 1970-2010 and found a total of 371 cases of PDC deficiency (88).

**Thiamine and magnesium**

The formation of TDP from thiamine requires magnesium, adenosine triphosphate (ATP) and the enzyme thiamine pyrophosphokinase (66). TDP dependent enzymes also require the presence of a divalent cation to achieve activation and magnesium has been demonstrated to provide optimal activation (89, 90). Although these aspects of the relationship between thiamine and magnesium have been well-understood biochemically for decades, the potential clinical relevance of such a relationship has received little attention to date (91, 92).

It is of interest that a recent NHANES study would suggest that two thirds of North Americans may be magnesium deficient (20, 47, 93). The RDA for magnesium is 320mg and 420mg for women and men respectively (47).

Dietary intake of magnesium may be subnormal by 65 – 220mg /day depending on geographic region (11, 93). Chronic ingestion of excessive amounts of sugar in the context of a micronutrient poor diet may, given the requirement for TDP and magnesium, results in altered metabolism (i.e. a dirty burn) (94). For example, obesity is also reported to be associated with magnesium deficiency (95-99). Intracellular magnesium also plays a key role in regulating insulin action, insulin-mediated-glucose-uptake and vascular tone (95, 98, 100, 101). Several epidemiologic studies have shown that adults and children consuming a western
type diet are consuming 30 – 50% of the RDA for magnesium (47, 93, 102). This
deficiency appears to be predominantly subclinical and therefore not routinely
investigated (11, 94, 103, 104).

Furthermore, the measurement of magnesium in the blood is
problematical since it is recognized to be perturbed by the systemic
inflammatory response (105), and measurable serum magnesium accounts for
only 0.15% of total body magnesium. As a result, serum concentrations are likely
to poorly reflect intracellular magnesium reserves (11, 103, 106). Finally, the
accepted normal range was originally described among a population who may
have been deficient (11, 106-109).

It is therefore of interest that recent meta-analyses and cohort studies
have pointed to an inverse relationship between magnesium consumption and
the incidence of NIDDM / metabolic syndrome (95, 110-121) and that a recent
prospective randomized controlled trial has demonstrated enhanced insulin
sensitivity in a population of 128 obese patients with confirmed
hypomagnesemia, chronic renal impairment and impaired glucose tolerance, in
response to magnesium supplementation (365 mg per day for three months
duration) (122). A similar study in a smaller sample size (n=72) of obese
patients with metabolic syndrome, confirmed reduced baseline intracellular
(monocyte) magnesium concentrations in 36% of obese patients but did not
report any improvement in markers of insulin resistance in response to
magnesium supplementation (400 mg per day for three months duration),
however potential compliance issues and a small study sample render these
results less reliable (123). Navarette-Cortes et al also reported no change in
indices of glucose control from a small (n=56) cross-over double blind prospective randomized controlled trail of normomagnesemic NIDDM patients in response to magnesium supplementation (365 mg per day for three months duration) (124).

Also, despite the limitations of the serum magnesium concentration, Bertinato et al have recently reported from an age stratified population based study of 5,446 participants, that up to 16% of the Canadian population had a serum magnesium concentration below the lower cut off of the population based reference range 0.75 – 0.95 mmol/L as defined by the NHANES group (109), and that serum magnesium concentration negatively correlated with diabetes and indices of insulin resistance and glycemic control (125).

Overall, when thiamine deficiency is considered with magnesium, it is likely that the deficiency of one or both may affect the other and compromise glucose metabolism in the obese patient.

Compromised PDH activity and lactate production in obesity

Consistent with the above, it has been recognized for decades that lactate concentrations are chronically elevated in obese diabetic patients (126-129). Adipocytes are known to produce lactate and it is accepted that raised lactate precedes the onset of insulin resistance in obese patients (128, 130). In health, adipose tissue PDH activity is insulin responsive, while in vitro studies of PDH activity in adipocytes from obese and NIDDM patients have demonstrated a loss
of this responsiveness (131, 132). Thiamine deficiency compromises PDH activity (64), and therefore may mediate PDH resistance to insulin.

Compromised PDH activity results in a ‘dirty burn’ and the accumulation of lactate (73). Furthermore, lactate load is recognized to be proportionate to the mass of adipocytes (133), and the rate of lactate production has also been reported to be associated with the age of the adipocyte. Hence lactate production may be proportionate to the extent and duration of the obesity state (128).

Chronically elevated lactate therefore heralds the onset of insulin resistance and NIDDM (134).

Clearly, in the context of the present review, this may reflect progressive exhaustion of intracellular thiamine and / or magnesium reserves due to a sustained high caloric burden. This simple hypothesis may be readily tested in the obese population by examination of the relationship between thiamine, magnesium and lactate.

The implications of the above observations are several and profound, as subclinical thiamine and / or magnesium deficiency may render the individual more vulnerable to insulin resistance and oxidative stress in the acute or chronic disease state (135, 136).

With reference to chronic disease, it is recognized that an elevated BMI in the obese range is an established risk factor for diseases such as type 2 diabetes (T2DM), cardiovascular diseases, and many cancers (95, 137). Indeed, dietary intake of thiamine and magnesium and their circulating concentrations have been associated with lower risk of these conditions (95, 97, 114, 138-142). For example, Wu et al conducted a meta-analysis which indicates that circulating
magnesium levels are inversely associated with incidence of CHD, hypertension, and T2DM (114). Despite numerous reviews highlighting a potential role for magnesium in T2DM (95, 114, 138), no definitive study has been conducted to clarify the therapeutic potential of this widely available nutritional supplement in the treatment of T2DM and associated complications. Similarly, despite identification of widespread thiamine deficiency among patients with T2DM and promising pilot study data in relation to treatment of the metabolic complications of T2DM with thiamine (44, 142), the protective effect of thiamine supplementation remains unproven in a prospective randomised controlled trial setting.

Furthermore, the specific biological mechanism mediating the interface between obesity, thiamine, magnesium and these conditions is not yet clear and no study has examined the combined effect of thiamine and magnesium in this spectrum of chronic disease conditions.

**Conclusion**

In summary, there is evidence that obesity may be associated with thiamine deficiency. This may be due to a mismatch between caloric burden and function of thiamine dependent enzymes. Thiamine, in turn, requires magnesium to be in its active form TDP. TDP also requires magnesium to achieve activation of TDP dependent enzymes during metabolism of glucose. Thiamine and magnesium play a critical role in glucose metabolism and their deficiency may result in the accumulation of anaerobic metabolites including lactate.
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.
1. exp Bariatric Surgery/
2. exp Obesity/
3. (bariatric adj3 surg*).ti,ab.
4. obes*.ti,ab.
5. 1 or 2 or 3 or 4
6. exp Thiamine Deficiency/ or exp Thiamine Pyrophosphatase/ or exp Thiamine/ or exp Thiamine Pyrophosphate/ or exp Thiamine Monophosphate/ or exp Thiamine Triphosphate/
7. (thiamine or thiamin or vitamin B1).ti,ab.
8. 6 or 7
9. exp Magnesium/ or exp Magnesium Deficiency/
10. magnesium.ti,ab.
11. 9 or 10
12. 5 and (8 or 11)
13. exp Diabetes Mellitus, Type 2/
14. type 2 diabetes.ti,ab.
15. 13 or 14
16. non insulin dependent diabetes.mp.
17. non insulin dependent diabetes.ti,ab.
18. 16 or 17
19. metabolic syndrome.mp.
20. metabolic syndrome.ti,ab.
21. 19 or 20
22. 15 or 18 or 21
23. 22 and (8 or 11)
24. (5 or 22) and (8 or 11)
Appendix 2

1659 non-duplicate titles and abstracts reviewed

209 articles retrieved

Inclusion/Exclusion Criteria Applied: Human studies - observational or prospective randomised controlled trials, in vitro and ex vivo studies of adipocytes, epidemiological studies

142 articles included

Search sieves for literature search detailed in appendix 1 including hand searched references.
## Appendix 3

### Table 1. Summary of thiamine values presented in Bariatric Surgery papers

<table>
<thead>
<tr>
<th>Author</th>
<th>normal</th>
<th>male</th>
<th>female</th>
<th>'Lowest value'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrodeguas (ug/dl) (37)</td>
<td>3.8 - 12.2</td>
<td>2.8-3.6 ug/dl</td>
<td>1.2 - 3.6 ug/dl</td>
<td></td>
</tr>
<tr>
<td>Flancbaum (ug/dl) (38)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10.86 ug/dl.</td>
</tr>
<tr>
<td>Mayo clinic</td>
<td>70 - 180 nmol/l.</td>
<td>2.66 – 6 ug/dl</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thiamine conversion: 1 ug = 3 nmol
Reference

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AveragThiamine and Magnesium [Average daily consumption of Thiamine and Magnesium 2013-4].


105. Švagždienė M, Širvinskas E, Baranauskienė D, Adukauskienė D. Correlation of magnesium deficiency with C-reactive protein in elective cardiac surgery with cardiopulmonary bypass for ischemic heart disease. Medicina (Kaunas). 2015;51(2):100-6.


Figure 1(a) Normal glucose metabolism in the presence of normoxia and adequate micronutrient concentration i.e. ‘a clean burn’

Figure 1(b) Altered glucose metabolism due to compromised TDP dependent enzyme function i.e. ‘a dirty burn’