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1 **The role of thiamine dependent enzymes in obesity and obesity related**

2 **chronic disease states: a systematic review**

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22   **Abstract**

23   The WHO 2016 report indicates that worldwide obesity is rising, with

24   over 600 million people in the obese range (BMI>30). The recommended daily

25   calorie intake for adults is 2000 kcal and 2500 kcal for women and men

26   respectively. The average American consumes 3770 kcal/ day and the average

27   person in the UK consumes 3400 kcal/ day. With such increased caloric intake,

28   there is an increased load on metabolic pathways, in particular glucose

29   metabolism. Such metabolism requires micronutrients as enzyme co-factors. The

30   recommended daily allowance (RDA) for thiamine is 1.3mg/day and 0.5mg

31   thiamine is required to process 1000 kilocalories (kcal). Therefore, despite the

32   appearance of being overfed, there is now increasing evidence that the obese

33   population may nutritionally depleted of essential micronutrients. Thiamine

34   deficiency has been reported to be in the region of 16 – 47% among patients

35   undergoing bariatric surgery for obesity. Thiamine, in turn, requires magnesium

36   to be in its active form, thiamine diphosphate (TDP). TDP also requires

37   magnesium to achieve activation of TDP dependent enzymes, including

38   transketolase (TK), pyruvate dehydrogenase (PDH) and alpha-keto glutaric acid

39   dehydrogenase (AKGDH), during metabolism of glucose. Thiamine and

40   magnesium therefore play a critical role in glucose metabolism and their

41   deficiency may result in the accumulation of anaerobic metabolites including

42   lactate due to a mismatch between caloric burden and function of thiamine

43   dependent enzymes. It may therefore be postulated that thiamine and

44   magnesium deficiency are under-recognized in obesity and may be important in

45   the progress of obesity and obesity related chronic disease states. The aim of the

46   present systematic review was to examine the role of thiamine dependent

47   enzymes in obesity and obesity related chronic disease states.

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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

90   evolutionary environment (10-13). Total health-care costs attributable to

91   obesity and overweight are projected to double every decade to account for 16–

92   18% of total US health-care expenditure by 2030 (1).

93   Despite the appearance of being overfed, there is now increasing evidence

94   that this population is nutritionally depleted of essential micronutrients and

95   vitamins (14-16). In 2012 the National Research Council reported that >80%

96   Americans consumed a diet, which was deficient for vitamins and minerals (15,

97   17). The NHANES 3 study reported that multi-nutrient deficiencies were more

98   prevalent in those with a BMI in the obese range than in the normal population

99   (18-21). In the present review we will examine the role of thiamine, an essential

100   component in the metabolism of glucose, in patients with obesity.

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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

134   studies, case reports and animal studies were excluded. Supporting evidence was

135   provided by *in vitro* and *ex vivo* cellular studies of adipocytes in eligible human

136   studies. There were no language or date restrictions. A copy of articles that met

137   the inclusion criteria was obtained for full-text review. No article was

138   unavailable.

139

140   **Thiamine metabolism**

141   Thiamine (Vitamin B1) is a water-soluble vitamin, that is required for the

142   metabolism of glucose (23). Thiamine is commonly found in meat (particularly

143   pork), eggs, fish and whole grains (23). Indeed, legislation in the United States

144   and Australia requires that certain staple foods, such as bread, be fortified with

145   thiamine (24). Many 'breakfast cereal' type foods are also supplemented (25, 26),

146   and 'over the counter' thiamine containing multivitamins are now widely

147   available (27).

148   Under normal physiological and nutritional conditions, the average adult

149   human has approximately a 3-week reserve of thiamine in the liver. It is

150   postulated that these reserves become rapidly depleted in disease, surgery or

151   times of sustained physiological stress (28-33).

152   The measurement of thiamine in red blood cells is known to reflect

153   nutritional status, and is not perturbed by the systemic inflammatory response

154   (34-36). Therefore, it is of interest that thiamine deficiency has been reported to

155   be in the region of 16 – 29% among patients undergoing bariatric surgery for

156   obesity (37-39), and this deficiency was reported to be even higher (31 – 47%)

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157 among some ethnic groups (15, 38). These findings are endorsed by a cross-

158 sectional study of thiamine consumption in a population of 1,100 Mexican-

159 American children, generated from NHANES data, which reported that thiamine

160 consumption may be inversely associated with obesity in that group (40).

161   Thiamine deficiency has also been reported to be present in up to 75% of

162 both type 1 and type 2 diabetics (41), and urinary excretion of thiamine has been

163 reported to be 24 times higher in Type 1 diabetes and 16 times higher in type 2

164 diabetes as compared to normal controls (41). Hence, thiamine deficiency has

165 been proposed as a mediator of insulin resistance and loss of oxidative resilience

166 in diabetes (42).

167   A pilot cross-over prospective randomized controlled trail (PRCT) (n= 12)

168 reported that thiamine supplementation (100mg taken three times per day for 6

169 weeks) resulted in significant decrease in 2-h plasma glucose relative to baseline

170 (8.78 +/- 2.20 vs. 9.89 +/- 2.50 mmol/l, p = 0.004) (43). It has also been reported

171 that thiamine supplementation may exert a nephro-protective effect in NIDDM

172 patients with evidence of early stage diabetic nephropathy and pilot studies have

173 yielded encouraging results (44, 45).

174   Given that the recommended daily allowance for thiamine is 1.3mg/day,

175 and that the average daily intake of thiamine from food for American adults is

176 1.87mg and 1.39mg in men and women respectively (46), and from the

177 combination of food and supplements is 4.90 in both men and women (47), it is

178 perhaps surprising that there are reported deficiencies in the obese. However,

179 the current recommended daily allowance for thiamine is based on studies

180 undertaken in the 1930's on healthy volunteers (48). At this time daily calorie

181   intakes were far lower than today. Nevertheless, from this work it may be

182   assumed that 0.5mg thiamine is required to process 1000kcal (kcal) (18, 23, 49).

183   On the basis of a 4000 kcal/day intake, it might be expected that an appropriate

184   RDA would be 2.0 mg /day. However, this would assume a linear relationship

185   between calories consumed and thiamine requirement.

186

187   **Pre-bariatric surgery related evidence of thiamine deficiency**

188   A comprehensive literature search reveals 53 case reports describing the

189   development of Wernicke's encephalopathy in patients during the post-

190   operative period following bariatric surgery. It is therefore surprising that there

191   are only five studies published that sought to quantify the extent of pre-

192   operative thiamine deficiency in patients undergoing bariatric surgery (37-39,

193   50, 51). Nath *et al* report a 16.5% prevalence of preoperative thiamine deficiency

194   (39). Carrodeguas *et al* and Flancbaum report a prevalence of 15.5% and 29%

195   low thiamine concentrations in obese patients prior to bariatric surgery

196   respectively (37, 38). Peterson *et al* also report significant thiamine deficiency in

197   patients prior to bariatric surgery, and note a significant racial disparity

198   (patients of Hispanic origin = 33%), which is in keeping with the ethnic

199   preponderance reported by Flancbaum *et al* (38, 50). Aron-Wisnewsky et al

200   report a preoperative prevalence of thiamine deficiency among 23% of the 22

201   women who underwent weight reduction surgery at their center (51).

202   However, it is worth noting that both Aron-Wisnewsky *et al* and

203   Flancbaum *et al* reported their results based on measurement of serum thiamine

204   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 measuremed, 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

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229 appendix 3) (37, 38, 58). Indeed, one of the studies provided no specific values of

230 whole blood thiamine concentrations, however this study does correlate clinical

231 criteria of symptoms related to thiamine deficiency with biochemically proven

232 deficiency measured in whole blood (i.e. red cell thiamine diphosphate) (38).

233   Overall, there is some evidence of an association between thiamine

234 deficiency and obesity, however given the scale of the problem there is a relative

235 paucity of robust data available describing thiamine status in obese patients.

236 This is surprising for a patient group who are known to be at risk of manifesting

237 clinical signs of thiamine deficiency in the postoperative period after undergoing
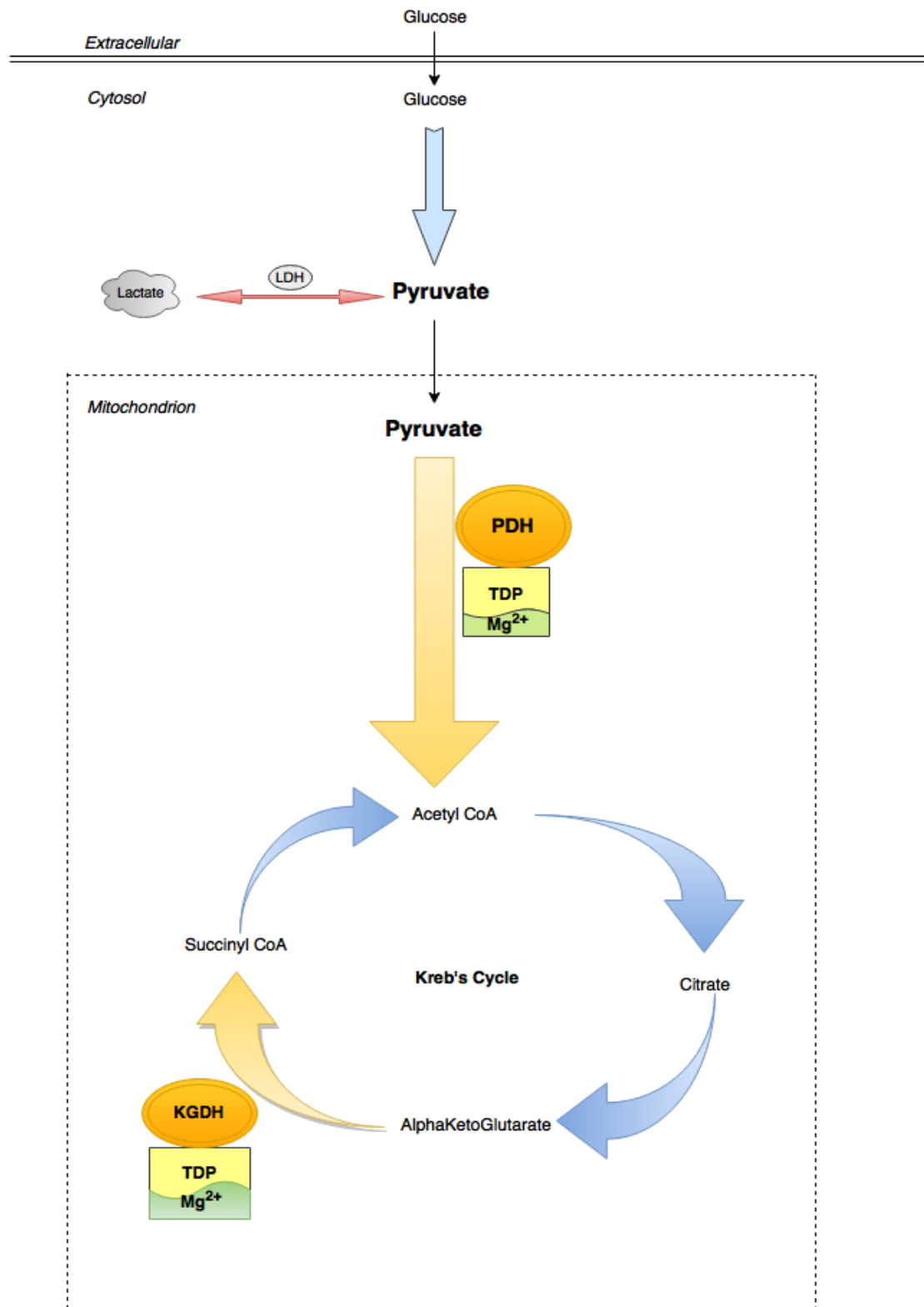
238 bariatric surgery (51, 59-63).

239

240 **The role of thiamine in glucose metabolism**

241   In the obese patient, most calories are in the form of glucose and there are

242 several key enzymes that require thiamine as a co-factor (64-66). Briefly, a

243 glucose load causes the pancreas to secrete insulin (67). Insulin causes the

244 expression of GLUT receptor transporters on the membrane of non-endothelial

245 and non-mesenchymal cells (68, 69). Glucose is taken into the cell where it is

246 metabolized to pyruvate via the glycolytic pathway (70, 71). Under ideal

247 conditions pyruvate enters the mitochondrion and is converted to Acetyl-CoA

248 through the action of pyruvate dehydrogenase (PDH) (64). Acetyl-CoA combines

249 with oxaloacetate to form citrate and thence through the action of alpha

250 ketoglutaric acid dehydrogenase (KGDH), generates ATP via the (Kreb's)

251 Tricarboxylic Acid (TCA) cycle (64). This may be considered to be the optimal

252 metabolism of glucose i.e. 'a clean burn'.

253   Thiamine in the form of thiamine diphosphate (TDP) (also known as

254   thiamine pyrophosphate) is required as a co-factor for pyruvate dehydrogenase

255   (PDH) and alpha ketoglutaric acid dehydrogenase (KGDH), both key enzymes for

256   the TCA cycle. Therefore, thiamine deficiency compromises these enzymes and

257   results in an altered metabolism of glucose.

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Glucose

Extracellular

Cytosol   Glucose

Lactate ⟷ LDH ⟷ **Pyruvate**

Mitochondrion

Pyruvate

PDH

TDP
Mg^{2+}

Acetyl CoA

Succinyl CoA

Kreb's Cycle

Citrate

KGDH

TDP
Mg^{2+}

AlphaKetoGlutarate

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260

261   *Figure 1(a)* Normal glucose metabolism in the presence of normoxia and

262   adequate micronutrient concentration i.e. *'a clean burn'*

263   Thiamine deficiency compromises PDH activity, hence pyruvate is unable to

264   gain access into the mitochondrion for conversion to acetyl-CoA and thereby

265   onto the TCA cycle (64). The resulting 'glut' of pyruvate in the cytosol triggers

266   up-regulation of lactate dehydrogenase (LDH) activity (72). LDH mediates the

267   increased production of lactate, which accumulates in the cytosol (73). This may

268   be considered to be the suboptimal metabolism of glucose i.e. 'a dirty burn'.

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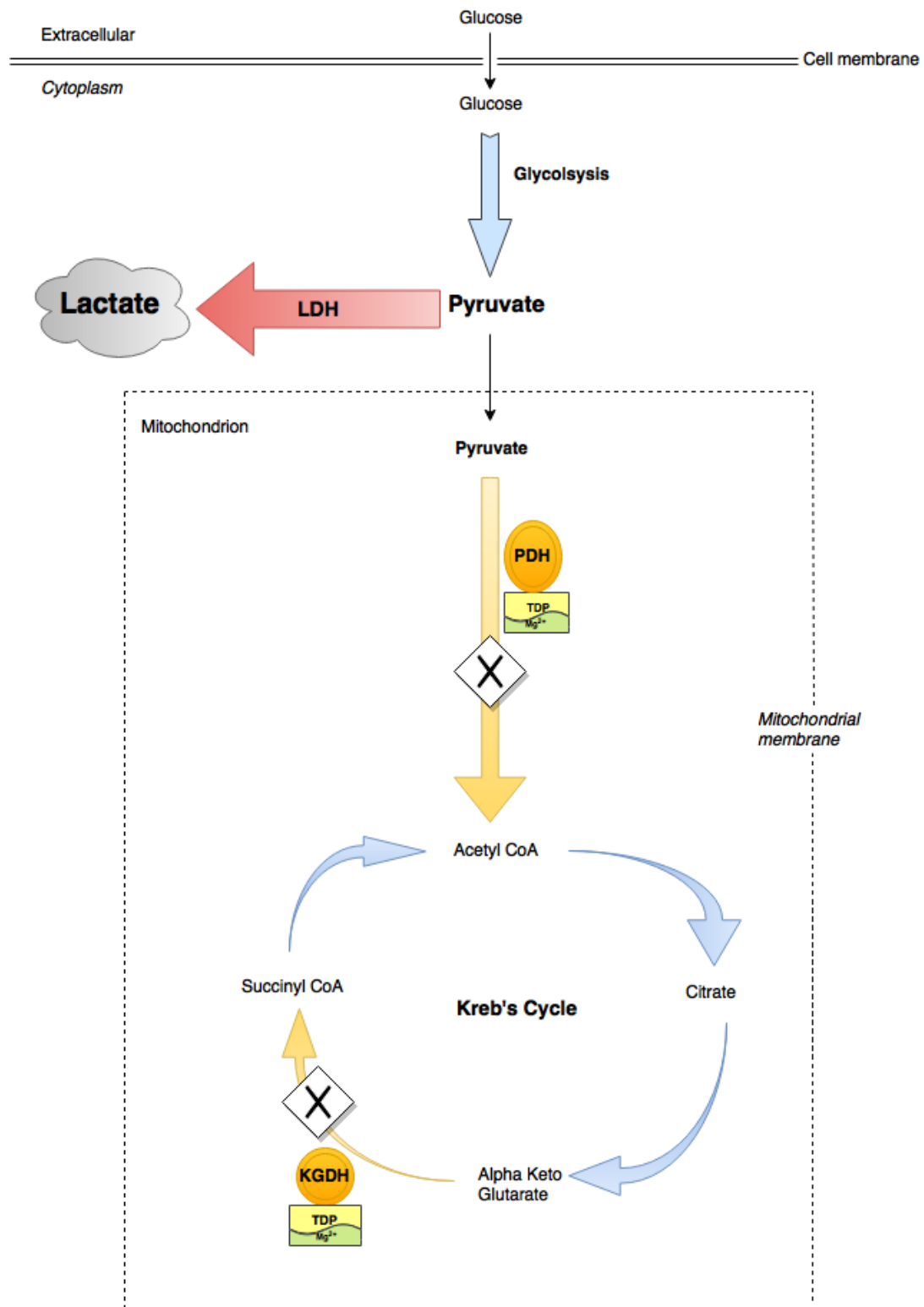
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Figure 1(b) Altered glucose metabolism due to compromised TDP dependent

enzyme function i.e. *'a dirty burn'*

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Pentose Phosphate Pathway, lactic acid and fatty acid synthesis

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275   The Pentose Phosphate Pathway (PPP) is a cytoplasmic pathway composed

276   of two arms: one irreversible and the other reversible. The irreversible arm is

277   oxidative and generates NADPH that plays a vital role in maintaining the cellular

278   redox balance. NADPH provides essential redox potential for synthetic pathways

279   e.g. fatty acid synthesis. The reversible arm is non-oxidative and links the

280   products of the irreversible arm back into the glycolytic pathway (74).

281   The 'glut' of pyruvate generated by suboptimal PDH activity may cause

282   diversion of glucose metabolism into the oxidative arm of the PPP (74, 75). This

283   increased flux through the oxidative arm of the PPP may then generate a net

284   excess of NADPH (75, 76). Interestingly, the conversion of pyruvate to lactate by

285   LDH also requires the conversion of NADPH to $NADP^+$, and excess of NADPH may

286   therefore drive the reaction towards increased production of lactate (72, 77).

287   Furthermore, fatty acid synthesis requires the conversion of NADPH to $NADP^+$;

288   hence excess NADPH may also facilitate increased fatty acid synthesis (76, 78).

289   The significance of a sustained elevation of serum lactate concentration is well

290   recognized as a marker of compromised oxidative resilience in the acute setting,

291   and as such has an established prognostic value. The threshold of normality for

292   blood lactate concentration is < 2.0 mmol/L. A recent publication by Varis et al

293   highlights the finding that a concentration >2 mmol/L among patients admitted

294   to an Intensive Care Unit (ICU) is consistently associated with a higher 90-day

295   mortality than a lactate concentration ≤2 mmol/L (43% vs. 22%) (79).

296   Furthermore, patients who continue to manifest hyperlactatemia (>2 mmol/L) at

297   ≥72 hours post admission to ICU are reported to have more than double the 90-

298 day mortality when compared with those patients whose lactate concentration

299 has resolved to ≤2.0 mmol/L at the same time point (52% vs. 24%) (79). Chronic

300 low-grade elevation of serum lactate concentrations at the upper limit of normal

301 may therefore indicate a reduced oxidative reserve and an increased

302 vulnerability to systemic insult and oxidative stress. Pepper et al conducted a

303 systematic review and meta analysis of the correlation between mortality and

304 elevated BMI among patients admitted to ICU (80). This highlighted the counter-

305 intuitive perspective of the 'obesity survival paradox' by revealing that a BMI in

306 the over-weight and obese ranges (BMI= 25 – 30 and 30 - 35 kg/m^2) may be a

307 protective factor for patients admitted to ICU with a diagnosis of sepsis, while a

308 BMI in the morbidly obese range (BMI > 35 kg/m^2) does not reduce mortality

309 (80). However, this meta-analysis was contradicted by a more recent and larger

310 meta-analysis conducted by Wang et al, which found that overweight, but not

311 obesity or morbid obesity, was associated with lower mortality in patients

312 admitted to ICU with a diagnosis of sepsis (80).

313   The implications of the thiamine deficiency state also extend directly to the

314 non-oxidative reversible arm of the PPP. Transketolase (TK) is also a TDP

315 dependent enzyme, which catalyzes the reversible arm of the PPP (81). Indeed, it

316 is this enzyme which has shown promise for combined co-factor

317 supplementation with magnesium (82). Compromised TK activity results in the

318 accumulation of a precursor to nucleotide synthesis, ribose-5- phosphate (83).

319 Indeed, accumulation of ribose-5-phosphate may serve to drive the process of

320 cell division.

321

Genetic variation in thaimine tansporters 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,

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346 Patel *et al* reviewed the literature published between 1970-2010 and found a

347 total of 371 cases of PDC deficiency (88).

348

349 **Thiamine and magnesium**

350   The formation of TDP from thiamine requires magnesium, adenosine

351 triphosphate (ATP) and the enzyme thiamine pyrophosphokinase (66)*.* TDP

352 dependent enzymes also require the presence of a divalent cation to achieve

353 activation and magnesium has been demonstrated to provide optimal activation

354 (89, 90). Although these aspects of the relationship between thiamine and

355 magnesium have been well-understood biochemically for decades, the potential

356 clinical relevance of such a relationship has received little attention to date (91,

357 92).

358   It is of interest that a recent NHANES study would suggest that two thirds

359 of North Americans may be magnesium deficient (20, 47, 93). The RDA for

360 magnesium is 320mg and 420mg for women and men respectively (47).

361 Dietary intake of magnesium may be subnormal by 65 – 220mg /day depending

362 on geographic region (11, 93). Chronic ingestion of excessive amounts of sugar in

363 the context of a micronutrient poor diet may, given the requirement for TDP and

364 magnesium, results in altered metabolism (i.e. a dirty burn) (94). For example,

365 obesity is also reported to be associated with magnesium deficiency (95-99).

366 Intracellular magnesium also plays a key role in regulating insulin action,

367 insulin-mediated-glucose-uptake and vascular tone (95, 98, 100, 101). Several

368 epidemiologic studies have shown that adults and children consuming a western

369   type diet are consuming 30 – 50% of the RDA for magnesium (47, 93, 102). This

370   deficiency appears to be predominantly subclinical and therefore not routinely

371   investigated (11, 94, 103, 104).

372   Furthermore, the measurement of magnesium in the blood is

373   problematical since it is recognized to be perturbed by the systemic

374   inflammatory response (105), and measurable serum magnesium accounts for

375   only 0.15% of total body magnesium. As a result, serum concentrations are likely

376   to poorly reflect intracellular magnesium reserves (11, 103, 106). Finally, the

377   accepted normal range was originally described among a population who may

378   have been deficient (11, 106-109).

379   It is therefore of interest that recent meta-analyses and cohort studies

380   have pointed to an inverse relationship between magnesium consumption and

381   the incidence of NIDDM / metabolic syndrome (95, 110-121) and that a recent

382   prospective randomized controlled trial has demonstrated enhanced insulin

383   sensitivity in a population of 128 obese patients with confirmed

384   hypomagnesemia, chronic renal impairment and impaired glucose tolerance, in

385   response to magnesium supplementation (365 mg per day for three months

386   duration) (122). A similar study in a smaller sample size (n=72) of obese

387   patients with metabolic syndrome, confirmed reduced baseline intracellular

388   (monocyte) magnesium concentrations in 36% of obese patients but did not

389   report any improvement in markers of insulin resistance in response to

390   magnesium supplementation (400 mg per day for three months duration),

391   however potential compliance issues and a small study sample render these

392   results less reliable (123). Navarette-Cortes *et al* also reported no change in

393   indices of glucose control from a small (n=56) cross-over double blind

394   prospective randomized controlled trail of normomagnesemic NIDDM patients

395   in response to magnesium supplementation (365 mg per day for three months

396   duration) (124).

397   Also, despite the limitations of the serum magnesium concentration,

398   Bertinato *et al* have recently reported from an age stratified population based

399   study of 5,446 participants, that up to 16% of the Canadian population had a

400   serum magnesium concentration below the lower cut off of the population based

401   reference range 0.75 – 0.95 mmol/L as defined by the NHANES group (109), and

402   that serum magnesium concentration negatively correlated with diabetes and

403   indices of insulin resistance and glycemic control (125).

404   Overall, when thiamine deficiency is considered with magnesium, it is

405   likely that the deficiency of one or both may affect the other and compromise

406   glucose metabolism in the obese patient.

407

408   **Compromised PDH activity and lactate production in obesity**

409   Consistent with the above, it has been recognized for decades that lactate

410   concentrations are chronically elevated in obese diabetic patients (126-129).

411   Adipocytes are known to produce lactate and it is accepted that raised lactate

412   precedes the onset of insulin resistance in obese patients (128, 130). In health,

413   adipose tissue PDH activity is insulin responsive, while *in vitro* studies of PDH

414   activity in adipocytes from obese and NIDDM patients have demonstrated a loss

20

415 of this responsiveness (131, 132). Thiamine deficiency compromises PDH

416 activity (64), and therefore may mediate PDH resistance to insulin.

417 Compromised PDH activity results in a 'dirty burn' and the accumulation of

418 lactate (73). Furthermore, lactate load is recognized to be proportionate to the

419 mass of adipocytes (133), and the rate of lactate production has also been

420 reported to be associated with the age of the adipocyte. Hence lactate production

421 may be proportionate to the extent and duration of the obesity state (128).

422 Chronically elevated lactate therefore heralds the onset of insulin resistance and

423 NIDDM (134).

424 Clearly, in the context of the present review, this may reflect progressive

425 exhaustion of intracellular thiamine and / or magnesium reserves due to a

426 sustained high caloric burden. This simple hypothesis may be readily tested in

427 the obese population by examination of the relationship between thiamine,

428 magnesium and lactate.

429 The implications of the above observations are several and profound, as

430 subclinical thiamine and / or magnesium deficiency may render the individual

431 more vulnerable to insulin resistance and oxidative stress in the acute or chronic

432 disease state (135, 136).

433 With reference to chronic disease, it is recognized that an elevated BMI in

434 the obese range is an established risk factor for diseases such as type 2 diabetes

435 (T2DM), cardiovascular diseases, and many cancers (95, 137). Indeed, dietary

436 intake of thiamine and magnesium and their circulating concentrations have

437 been associated with lower risk of these conditions (95, 97, 114, 138-142). For

438 example, Wu et al conducted a meta-analysis which indicates that circulating

439   magnesium levels are inversely associated with incidence of CHD, hypertension,

440   and T2DM (114). Despite numerous reviews highlighting a potential role for

441   magnesium in T2DM (95, 114, 138), no definitive study has been conducted to

442   clarify the therapeutic potential of this widely available nutritional supplement

443   in the treatment of T2DM and associated complications. Similarly, despite

444   identification of widespread thiamine deficiency among patients with T2DM and

445   promising pilot study data in relation to treatment of the metabolic

446   complications of T2DM with thiamine (44, 142), the protective effect of thiamine

447   supplementation remains unproven in a prospective randomised controlled trial

448   setting.

449   Furthermore, the specific biological mechanism mediating the interface

450   between obesity, thiamine, magnesium and these conditions is not yet clear and

451   no study has examined the combined effect of thiamine and magnesium in this

452   spectrum of chronic disease conditions.

453

454   **Conclusion**

455   In summary, there is evidence that obesity may be associated with

456   thiamine deficiency. This may be due to a mismatch between caloric burden and

457   function of thiamine dependent enzymes. Thiamine, in turn, requires magnesium

458   to be in its active form TDP. TDP also requires magnesium to achieve activation

459   of TDP dependent enzymes during metabolism of glucose. Thiamine and

460   magnesium play a critical role in glucose metabolism and their deficiency may

461   result in the accumulation of anaerobic metabolites including lactate.

462   It may therefore be postulated that thiamine and magnesium deficiency are

463   under-recognized in obesity and may be important in the progress of obesity and

464   obesity related chronic disease states.

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482 **Appendix 1.**

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)

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491   **Appendix 2**

492

Medline: 1744 titles and abstracts reviewed

Google scholar

NHANES

Cochrane

Hand searched and translated = 3

1659 non-duplicate titles and abstracts reviewed

209 articles retrieved

Inclusion/ExclusionCriteria Applied: Human studies - observational or prospective randomised controlled trials, in vitro and ex vivo studies of adipocytes, epidemiological studies
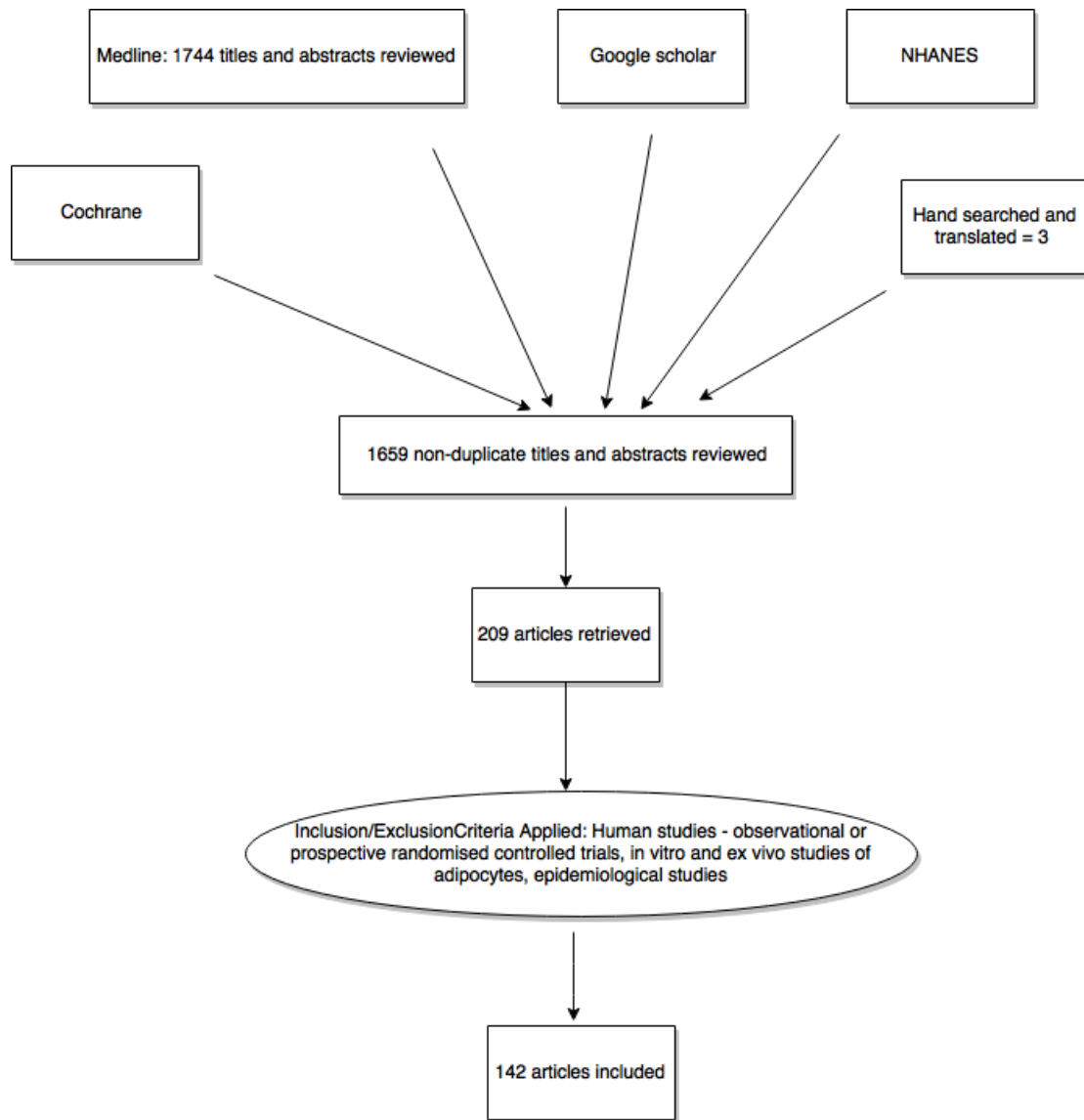
142 articles included

493

494   Search sieve for literature search detailed in appendix 1 including hand searched

495   references

496

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498

499   **Appendix 3**

500

Author	normal	male	female	'Lowest value'
Carrodeguas (ug/dl) (37)	3.8 - 12.2	2.8-3.6 ug/dl	1.2 - 3.6 ug/dl	
Carrodeguas (nmol/l) (37)	114 – 366	84 – 108 nmol/l.	36 – 108 nmol/l.	
Flancbaum (ug/dl) (38)	-	-	-	10.86 ug/dl.
Mayo clinic	70 - 180 nmol/l. 2.66 – 6 ug/dl			

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

502   Thiamine conversion: 1ug = 3 nmol

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Reference

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929   *Figure 1(a)* Normal glucose metabolism in the presence of normoxia and

930   adequate micronutrient concentration i.e. *'a clean burn'*

931   *Figure 1(b)* Altered glucose metabolism due to compromised TDP dependent

932   enzyme function i.e. *'a dirty burn'*

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