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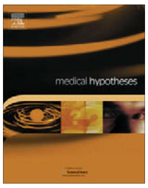

The straight line hypothesis elaborated: Case reference obesity, an argument for acidosis, oxidative stress, and disease conglomeration?

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SUMMARY

Studies report on the association between obesity and oxidative stress, with and without additional diseases. Macrophages in adipocytes, and hypoxia in adipose tissue have been suggested to explain how obesity can relate to oxidative stress. The straight line hypothesis using the lactic acid trap construct has been put forward to explain how proton imbalance can relate to obesity. Proton imbalance has been also reported to associate with the production of reactive oxygen species by inhibition of mitochondrial energy production. This review brings together existing literature and concepts to explain how obesity can relate to oxidative stress via protons, uniquely for itself or, as often observed, in conglomeration of additional diseases.

Introduction

The straight line hypothesis of diet, acidosis, diseases-aging (henceforth the straight line hypothesis; SLH) put forward how protons (H+) and their imbalance could relate to obesity [1]. Obesity is known to be caused by many factors: life-style, behavior, metabolism, genetics, etc. [2]. Obesity has been also related to other diseases, such as, hypertension, diabetes type 2, cardiovascular diseases, etc. [3]. The immune response has been proposed as a central homeostatic mechanism in operation for the occurrence of these diseases in a bundle [3]. How this occurs, however, is yet to be delineated [3].

The relationship of obesity with oxidative stress, with and without additional diseases, is also currently under investigation [4–6]. Various theories have been put forward to explain this nexus. A comprehensive list of these mechanisms can be read in a review by Surmi and Hasty [5]. In this review some of these theories [7–9] will be taken up, where a support for the role of H+ is indicated.

This review opens with an introduction on the existing theories explaining the relationship of obesity with oxidative stress. Section “Connections between obesity and oxidative stress” also introduces the relationship of H+ with oxidative stress in obesity. Section “Elementary mechanisms of oxidative stress” picks up the possible role of H+ from view-points of diet and mitochondrial energy production. In the final section “Proton imbalance and oxidative stress”, the individual elements of preceding sections are brought together, with support from empirical literature, to present the case of relationship of H+ with oxidative stress, and with disease conglomeration. The review concludes with a point summary of the salient.

Connections between obesity and oxidative stress

Association between obesity and oxidative stress was reported uniquely for itself [4,6,10] and in relation to specific diseases, e.g., insulin resistance, diabetes, cardiovascular diseases, and polycystic ovary syndrome [3,10–12]. Obesity has been also related to oxidative stress, both in young and old [6], even so aging itself is also directly associated with oxidative stress [13]. The relation between obesity and oxidative stress is thought to contribute to the development of inflammation and diseases, such as, insulin resistance, diabetes, etc. [3,9,11,14]. Oxidative stress occurs when the level of reactive oxygen species (ROS), i.e., organic and inorganic molecules containing oxygen as free radicals or peroxides, become very high. Macrophages, neutrophils, and lymphocytes produce ROS against microbes. Paracrines, e.g., interleukins (IL) (IL-1, IL-6, tumor necrosis factor alpha [TNF-alpha]) are released by macrophages, alert the immune system, and promote an inflammation when an infection is present. This functions as the body’s immune response (defense). What presents a problem is an oxidative stress as an autoimmune response. The discussion of obesity with respect to oxidative stress takes place perhaps in this context. IL-1, TNF-alpha, etc. are, hence, often referred to as proinflammatory cytokines, and when these protein molecules are found in adipose tissue they are also called adipokines.

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Macrophages

A longitudinal study on severely obese women reported that oxidative stress decreased as adipose tissue decreased during a weight loss program [4]. This direct association between obesity and oxidative stress is probably best explained by the structural existence of macrophages and T lymphocytes in adipose tissue using mouse models [8,9]. Macrophages are most tissue ubiquitous, fulfilling a normal, phagocytic function in various body tissues [15]. Weisberg and colleagues [8] delineated that macrophages (which till then were without any explained function in the adipose tissue) tend to accumulate in adipocytes in direct proportion to the size of adipocyte and cause inflammation. The study reported that obese mice had a greater macrophage infiltration in adipose tissue compared to lean. A corollary, independent study by Xu–Barnes and colleagues [9] reported a significant upregulation of genes coding for macrophages in white adipose tissue, but not in muscle, liver, lung, and spleen tissues (no significant change either in gene or messenger RNA expression) in obese mice. The inflammation response observed was restricted to white adipose tissue. This group suggested that leptin could mediate the recruitment of macrophages in adipose tissue. Surmi and Hasty [5] proposed a probable mediation over leptin as well, since it has been reported to work as a chemoattractant for monocytes and macrophages [16], for neutrophils [17], and for cancer cells [18]. Leptin is known to correlate with the amount of adipose tissue [19] but morbid obesity in mice and human has been also reported in leptin deficiency [5]. A study showed that in obese mice genetic variations affected insulin responses, but once the genetic variation was controlled, a leptin deficiency had variable effects on obesity in combination with diabetes [20]. The research group reported mice (DBA-ob/ob) with low insulin had greatly diminished adiposity with atrophied islets, whereas, mice (DBA-ob/ob) with high insulin maintained adiposity with an increase in beta-cells [20]. Insulin, itself, is known to be an anabolic hormone [21]. Further work is required in filtering out how insulin and leptin mediate the reported association of obesity with oxidative stress in relation to genetic variation.

To summarize, the two seminal studies by Weisberg et al. and Xu–Barnes et al. offer a complementary mechanism explaining how obesity can relate to oxidative stress, i.e., over an accumulation of macrophages. ROS can effect DNA damage, peroxidize fatty acids [6], oxidize amino acids [6,13], and inactivate enzymes [22] up to cell apoptosis [23]. In adiposity related inflammation, it has been shown that the inflammation occurs after an increase in adiposity [8,9] but before occurrence of disease, specifically, insulin resistance [8,9].

Hypoxia

Another proposed mechanism in understanding the relationship of obesity and oxidative stress is via hypoxia. Apoptosis of adipocytes is said to occur due to hypoxia in a stage of rapid adipose tissue expansion [7]. This has been suggested to trigger macrophages infiltration into the adipose tissue [23]. In turn, the macrophages produce ROS and cytokines. Ye and colleagues [24] demonstrated that in adipose tissue hypoxia associated with increased expression of inflammatory genes and decreased expression of adiponectin in obese mice strains. A study mentioned that measurements at gene or mRNA level (transcription) alone, might not completely reflect net biological function due to the differences in translation and even post-translational processes [11] as the study by Chua et al. [20] corroborates. However, Ye and colleagues [24] demonstrated at an organism level (obese mice), that reduction in body weight by calorie restriction associated with an improvement in oxygenation and reduction in inflammation. Trayhurn et al. [7] explained that enlarged adipocytes distant from vasculature would suffer hypoxia leading to an inflammation. In a more recent study on mice and human adipocytes Trayhurn and colleagues [25] reported hypoxia [induced by low oxygen (O_2) or chemically] led to the stimulation of the expression and secretion of cytokines, such as, IL-6, leptin (adipokine), and macrophage migration inhibitory factor. That is, a hypoxia seems to stimulate an inflammatory response via macrophages.

An animal study reported that environmental hypoxia, characterized by pulmonary hypertension, right ventricular hypertrophy, with eventual heart failure and death, simulated in a rat strain related with chronic hypoxemia and not with hypobaric exposure per se. Importantly, addition of hypercapnia partially blunted hypoxia, with oxygen delivery to cells [26]. Trayhurn and colleagues showed that obesity related to endogenous hypoxia [7]. Taken together, if hypercapnia would coexist with hypoxia a probable explanation for the existence of obesity related hypoventilation syndrome (first described in 1955 by Achincloss, Cook, and Renzetti [27]) would be possible. At lower absolute oxygen intakes, compensated partially by hypercapnia and/or lower than average respiratory rate, as per the SLH, the condition is quite amenable with some amount of anaerobic lactic acid production in hypoxic tissues. In the longer run the endogenous hypoxia could relate to some amount of increase in ROS with time.

The SLH highlights hyperventilation and hypoventilation breathing responses [1] principally as it would be important to determine the underlying hypoxia and/or hypercapnia. Erbland and colleagues [28] showed that in normal subjects and patients with chronic obstructive pulmonary disease an increase in respiratory acidosis by increasing carbon dioxide (CO_2), greatly potentiated the increase in respiratory drive in response to hypoxia. This indicates that an SLH suggested acidosis might also relate to a hyperventilatory response, which for the units of CO_2 (volatile acid) excreted, could produce some lactic acid in cells again. An aerobic to anaerobic production of lactic acid could accompany this, though at higher oxygen intakes, which could also relate to ROS production with time.

The lactic acid construct, called the "lactic acid trap", would itself be also determined by diet, which could perpetrate a latent to metabolic acidosis [1]. At a lower to higher than normal oxygen intakes; a higher than usual partial oxidation of glucose (glycolysis only) could occur, effecting a lactic acid trap with partial tissue hypoxia under eucapnia to hypercapnia. The interaction of nutrition with tissue and respiratory breathing, indirectly also physical activity, requires investigation. Elaborations of this concept will be picked up again in Section "Mechanism of an altered mitochondrial energy production". What is known from literature is that exhaled breath pH is used as a biomarker for airway acidity, inflammation, and oxidative stress [29,30]. That is, just as obesity has been associated with oxidative stress [4–6,8,9], even H+ have been associated with oxidative stress [12,29–31]. Section "Connections between obesity and oxidative stress" recapitulates the current mechanisms on how obesity can relate to oxidative stress. Using SLH the section also introduces how these mechanisms can relate to disequilibrium in H+ in obesity which, in turn, relates to an oxidative stress.

Elementary mechanisms of oxidative stress

A study reported mice deficient in chloride–bicarbonate anion exchanger two had elevated intracellular H+ in splenocyte (splenic macrophage) with an increase in production of IL [32]. Another study showed that diabetic ketoacidotic patients, whether lean or obese, exhibited a comparable increase in oxidative stress, proinflammatory cytokines, and cardiovascular risk markers [12]. The ketoacidosis in diabetes, itself, is a condition of an increase in endogenous H+. Yet another study reported genetically obese strains exhibited both high insulin at adiposity, and low insulin at diminished adiposity [20]. Differences in expression of protein possibly involved in lipid and glucose metabolism, oxidative stress, and adipocyte differentiation was reported in the omental fat for morbidly obese women with polycystic ovary syndrome and those without the disease [11]. These studies go to suggest that ROS is usually higher in diseases, obesity being one of the many diseases. It also suggests existence of mechanisms more elementary than obesity that could be in operation in its relation to oxidative stress. Imbalance in H+ [12,29–36] could be one such mechanism which could operate for a given genotype at varying metabolome over environment (life-style). The next sub-sections will attend to this discussion.

Mechanism of an imbalance in nutrition

Disequilibrium in energy intake as proposed in the SLH can lead to disequilibrium in H+, thereby affecting energy oxidation status, which in turn can relate to onset of diseases, even aging [1]. Robertson and colleagues [37], using diabetes type 2, suggested a primary precedence of hyperglycemia; i.e., a hyperglycemia can occur without hyperlipidemia and precedes hyperlipidemia. Both propose a primacy of glucose metabolism, with or without changes in fatty acid metabolism [37,1]. The utilization of energy substrates, barring the unique role of acetyl coenzyme A (reversible in synthesis and degradation of lipids and amino acids but not in carbohydrates), are relatively independent pathways. A certain reciprocal up and down regulation in fuel source has been reported; best case example being the heart [38]. A study by Stentz and colleagues [12] reported that hyperglycemia and ketoacidosis induced changes independently in oxidative stress, cytokines, and cardiovascular risk. Hyperglycemia implies involvement of carbohydrate metabolism, whereas ketoacidosis implies an involvement of fatty acid metabolism, with or without involvement of carbohydrate metabolism. It is known that ketoacidosis can also occur in undernutrition [1], in addition to metabolic–genetic dysfunctions. Given a nutrition of plenty, as the average Western diet is, the chance of a primacy in carbohydrate metabolism preceding other changes seems plausible [1,37]. A study reported that the gene expression of glucose transporter (GLUT1), its protein level, and the glucose transport by human adipocytes were increased by hypoxia [25]. This led the research group to suggest glucose utilization is stimulated by hypoxia. Yet another study reported that in transgenic mice an overexpression of GLUT1 increased myocardial glucose uptake and oxidation, thereby lowering the flexibility in use of cardiac metabolic fuel, possibly making the heart susceptible to contractile dysfunction [38]. Cancers and vascular calcifications in nondiabetics have been also marked with higher expression of GLUT1; in case cancer thought to provide rapid energy to multiplying tumor cells [39–41]. To summate, hypoxia which might associate with a proton imbalance condition [28,33] could be associated with diseases; obesity being one of them, characterized by a higher glucose uptake. There emerges the concept of irregularities in glucose uptake, at normal to higher glucose supply (intake), by adipose, cancerous, and vascular calcification tissues, all of which can be generalized into tissue growth of excess, if not untoward.

Mechanism of an altered mitochondrial energy production

Acidosis, as in accumulation of H+, has been reported to inhibit mitochondrial energy production in humans and animals [42,43]. Mitochondrial energy production (MEP) [produces adenosine triphosphate (ATP)], where acetyl coenzyme A enters the citric acid cycle (Section "Mechanism of an imbalance in nutrition"), is coupled with oxygen consumption by the H+ electrochemical gradient in mitochondrial inner lining with byproducts of water (H_2O) and CO_2. Thus, electrons are passed through a series of proteins via oxidation–reduction reactions with final destination of O_2, which gets reduced to H_2O. This complete oxidation of glucose molecule is largely electroneutral compared to oxidation of fatty acids and total proteins, both of which be net acid producing via some amount of keto and sulfuric acid production.

Physical chemistry has long shown that ATP production from complete oxidation of glucose is not perfectly coupled. That is, there is minor H+ leak [44]. Incomplete reduction of oxygen ion (O_2^-) might produce superoxides, which physiologically are largely present as hydrogen peroxide (H_2O_2), a ROS. As per the Lowry–Bronsted definition of acid, H_2O_2 is a very weak acid in water but in alkaline solutions (endogenous pH ranges are largely alkaline) it will be deprotonated preferentially to H_2O and could result in cell damage. The O_2^- of H_2O_2 could also react with nitric oxide to produce peroxynitrite [45]. More damaging than this is the production of the hydroxyl ion (OH^-) [44] from H_2O_2 in presence of metal catalyst, known as the Haber–Weiss reaction (or Fenton reaction) [46]. The classical metal ion complex is iron (ferrous and ferric complex), though copper, chromium, nickel, cobalt and vanadium have been also studied. Thus, the role of excess metals in combination with ROS is an area requiring research too.

These changes have been explained using concepts of density functional theory [47] and the Hartree–Fock calculations [48]. Classically, the mitochondrial H+ leak is dealt with one-electron approach but the advent of ferryl species introduce the complexities of diradical intermediates, which are thought to lead to nonequilibriums, i.e., molecular configurations tend to be fragile [48,49]. An experiment reported no correlation between change in nuclear energy with acidities of Bronsted acid sites but a correlation between the change in nuclear energy and OH^- [50]. All these experimental results indicate the damaging property of ROS. Encompassing these results, it appears that in MEP, H+ leaks could divert electrons to ROS production, which in the presence of transitional metals as diradical intermediates could increase the propensity to nonequilibrium configurations perhaps inflicting greater cell damage. A certain amount of H+ leak occurs at so-called complete glucose oxidation. This means MEP is not 100% efficient, indicating rate of living explanation of aging [51] which explains part of the senescence process associated to ROS [13]. This concept is supported by a study result of an increase in H+ leak in situ mitochondria in hepatocytes from old rats compared to young rats [52]. The same study, however, also reported a greater H+ leak in isolated liver mitochondria from obese mice strains compared to lean controls [52]. This means H+ imbalance and oxidative stress can be associated also to diseases, e.g., obesity.

O_2 not entering the TCA cycle due to inhibition of MEP by H+ (at hypoventilation to hyperventilation with aerobic to anaerobic lactic acid production, both of which are an increase in H+; refer Section "Hypoxia") could be channeled to ROS production over and above the aging process. An O_2 paradox has been reported [53], i.e., the O_2 required to drive cellular processes (MEP) can also inhibit vital functioning. That is to say, with an excess glucose intake and/or uptake (environment and metabolome) undergoing only partial oxidation to produce lactic acid aerobically and/or anaerobically, would go alongside a risk to increase H+ (even at partial substrate diversion towards fat deposition for a given genotype), accumulation of which would inhibit MEP over and above the normal H+ leak implying an additional ROS burden (Fig. 1). That these changes might be triggered by a incipient accumulation of H+ via diet, mediated by tissue and respiratory breathing, remain to be tested. To summate, this section suggests that an underlying H+ imbalance, inherently or environmentally modified by breathing, could add to the ROS production while simultaneously inhibiting

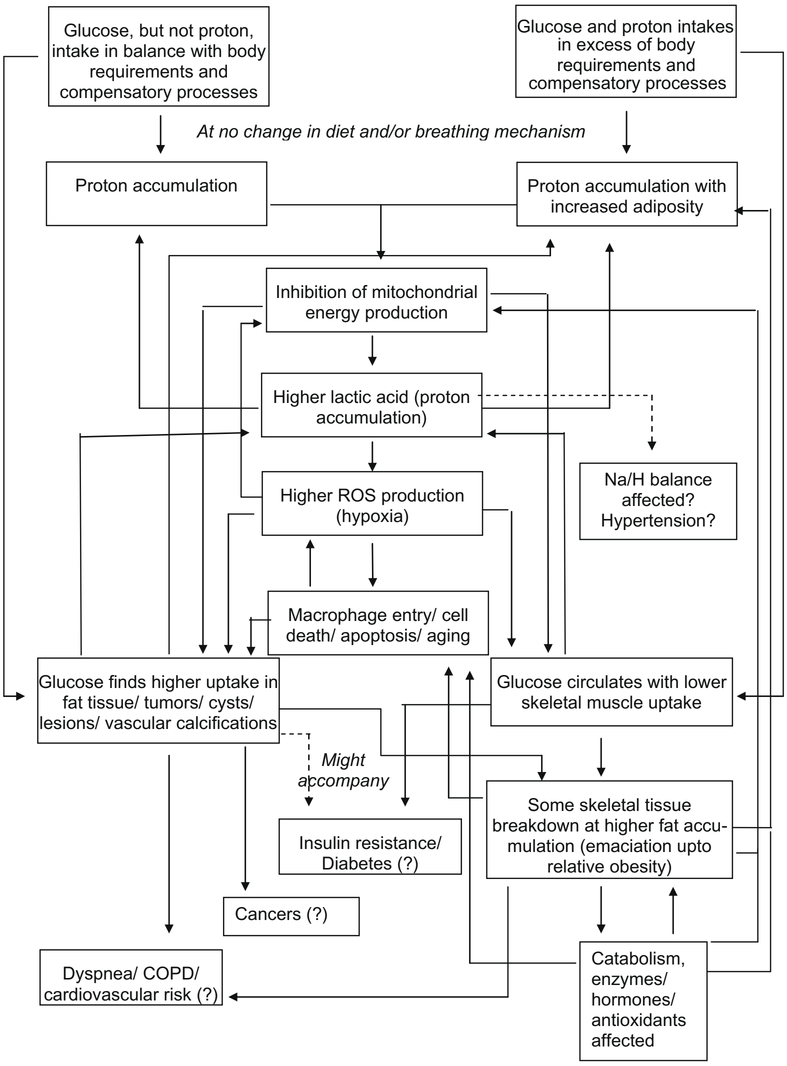

Fig. 1. An elaboration of the straight line hypothesis of diet, acidosis, diseases-aging.

MEP. In the next section, these process will be further brought in context to obesity and related diseases, often called the diseases of civilization.

Proton imbalance and oxidative stress

Studies reported higher ROS production across a whole spectrum of diseases, such as, insulin resistance and diabetes [37,54], rheumatoid arthritis and multiple sclerosis [55], polycystic ovary syndrome [11], cardiovascular diseases [3,22], cancers [56]. Section “Connections between obesity and oxidative stress” updates on obesity – uniquely for itself, and in combination with other diseases. A study by Ardevol and colleagues [57] using mice reported that both obese and lean mice had similar lactate (lactic acid) production after short intense exercise. However, in lean mice 17.2% of the lactate formation was in muscles and in obese mice only 4.4%. The difference in lactate production in obese mice was traced to its production in white adipose tissue. Thus, the group concluded with suggestion of a massive extra-muscular glycolysis because of early fatigue in obese rats due to bicarbonate exhaustion. It is known that dietary neutralized acids (with vegetables and fruits or dietary alkaline supplements) can ease renal H+ compensation, with indications also of easing respiratory H+ compensation [34], given healthy breathing dynamics [1]. Sections “Hypoxia and Mechanism of an altered mitochondrial energy production” proposed how a lactic acid trap can operate under aerobic and anaerobic conditions coupled with inefficient ATP production, which can be amenable with excess tissue growth (adipose, tumor, cysts, vascular calcifications, etc.) under local hypoxia, with or without an accompanying hypoventilation to hyperventilation (even dyspnea), as while O_2^-, which originally meant for MEP, could be channeled to ROS at higher H+ (Fig. 1).

A greater glucose uptake by myocardial cells which might relate to increasing the heart susceptibility to contractile dysfunction has been reported [38]. A greater glucose uptake by fat cells [25], cancerous cells and vascular calcifications [39–41] has been also reported. However, such an increased glucose uptake has not been reported for the cells of the skeletal muscle [57], which is actually the tissue of major MEP production. Infact, Ardevol and colleagues [57] indirectly show that glucose uptake in skeletal muscles in obese mice was extremely lower than in the not obese. The mechanism of a lower glucose uptake by skeletal muscles is still unclear. However, the issue questions that if skeletal muscle uptake is lower than normal, could the glucose be longer in circulation, even at higher insulin secretion? Bundling of diseases with obesity has been reported [3]. Studies have also reported association between diabetes and oxidative stress [10,58]. Associations between diabetes and cancers have been also reported [59–62]. What these apparently different diseases seem to share is a common elementary pathway over H+ (SLH) visible with higher ROS.

It appears, thus, that energy production in obesity (diseases) can shift to lower equilibriums (efficiencies) given lactate production [57] as proposed by the lactic acid trap [1], while the glucose meant for skeletal tissue uptake might still be in circulation and/or finding greater uptake in excess to unwanted tissue growth; an area deserving immediate research attention (Fig. 1). To generalize, each biochemical reaction is pH dependent, hence, an imbalance in H+ can associate with long term changes in state of health status (aging, diseases) requiring evidence based research. These changes with time would be partially modifiable by attending to both dietary and respiratory lifestyles.

Point summary

- Direct association of obesity with oxidative stress, explained by infiltration of macrophages into adipose tissue, and hypoxia in adipose tissue.
- Greater glucose uptake by adipose tissue (at rapid tissue expansion with hypoxia) given glucose substrate availability.
- Glucose uptake by skeletal tissue in obesity reported to be lower than normal.
- Partial glucose oxidation associated with higher H+; H+ production over and above protein and fats related sulfuric and keto acids.
- Accumulation of H+ inhibits MEP, at varying breathing dynamics.
- Accumulation of H+ coupled to ROS production.
- ROS, in excess of antioxidants, brings about tissue damage and cell apoptosis.

Conflicts of interest

None declared.

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