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Review Article

Role of Micro-And Macro-Nutrients in Obesity Onset

Introduction

The incidence of obesity has been increasing exponentially for the last 30 years, and it is posing a major health issue in the US and worldwide. The 2015 reports by the World Health Organization (WHO) and the Center for Disease Control (CDC) in the US indicate that approximately 1.9 billion people worldwide are overweight and more than 600 million are frankly obese, irrespective of genders, races, ethnicities, ages, and socio-economic strata [1]. As individuals become obese or overweight at a younger age, the incidence and severity of obesity-related long-term complications has also increased significantly. Type 2-diabetes, particular forms of cancer (i.e. breast, ovarian, colon, and liver cancer), and cardiovascular diseases including hypertension and stroke represent the most common complications of obesity, and all carry expensive price-tags. In the particular case of diabetes, previous predictions estimating ~28 million people in the US to be affected by diabetes by the year 2030 have proven to be optimistic as 29.1 million individuals were reported to be diabetic by the year 2012, with an attached price-tag for the US healthcare system in excess of 250 billion USD between direct and indirect costs including lost productivity [2]. The trend continues unabated, with ~900,000 new cases of diabetes diagnosed every year in the US only [3]. In countries such as China, India, Saudi Arabia, UAE, etc. the increase is even steeper, and it predicts that more than 500 million individuals worldwide will be diabetic by the year 2030 [2]. These projections are an underestimate as pre-diabetic individuals may elude medical screening and go undiagnosed. More intriguing, epidemiologic and genetic studies indicate that specific ethnicities and races are more susceptible to develop obesity, diabetes, or hypertension, and show significant discrepancies between genders, with women being more significantly affected. For example, obesity affects ~57% of African-American women and ~46% of Hispanic women as compared to ~38% of African-American men, and ~39% of Hispanic men [1,2], raising the question as to whether particular genetic factors have been over-looked or under-estimated that can explain the higher propensity to obesity in women of these two ethnicities.

Because of the increasing incidence in obesity and associated diabetes, more medical and healthcare resources have been devoted to understand the reasons for the rampant increase in these pathologies, hoping to contain and possibly reverse the trend. From the therapeutic stand point, attempts to control weight gain through pharmacological approaches, life-style changes, and dietetic regiments, often in combination, have attained modest success due to costs, patient compliance, or inability/unwillingness by the patient to sustain the necessary efforts over time. Of concern, many individuals experience significant weight-gain rebound when the initial therapy or diet is discontinued for medical or personal reasons. Presently, bariatric surgery in its various approaches appear to be the only treatment able to provide significant and long-lasting weight loss [4]. However, this therapeutic approach remains of limited implementation mainly for its cost, its irreversibility (for many of the implemented procedures), and the limited knowledge about the long-term implications associated with major changes in the physiological gastro-intestinal absorption of minerals and nutrients. After several years of implementation, follow-ups on large numbers of patients who have undergone these procedures indicate the occurrence of gallstones, anemia, or osteoporosis, mostly as a result of nutritional deficiencies in more than 30% of the treated patients, especially if appropriate level of bile acid production, or vitamins and micronutrients intake [4] are not maintained.

Because of the large economic burden placed by obesity, diabetes, cancer, and cardiovascular complications on the health system of the affected countries, and the ineffectiveness of most medical or dietary treatments at controlling weight gain permanently, attention has shifted towards a better understanding of the nutritional requirements of a healthy, balanced diet, and the quality of the dietary nutrients, to determine whether the most commonly used diets (e.g. Weight

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Watchers, South Beach diet, Paleo diet, Atkins diet, etc.) provide an appropriate intake of micronutrients such as minerals, vitamins, antioxidants, and oxylipins, and macronutrients (e.g. proteins), as a more natural and effective approach to control weight gain. This approach has prompted a strong interest in understanding how various macro- and micro-nutrients contribute to whole body metabolism together with hormones like insulin and adipokines, to ultimately educate the general population on the most effective and beneficial diets.

As the physiological relevance of dietary micro-nutrients is not fully understood, this review will focus on zinc and magnesium deficiency, for which a more clear mechanistic correlation between mineral deficiency and the onset of obesity and its diabetic complications has been established. In addition, the relevance of a proper dietary protein intake will be discussed.

Dietary Zinc and Magnesium Intake and their Physiological Importance

Evaluation of the current status of obesity and its complications indicate that the cumulative number of years lost to obesity and obesity-related risk factors is about three times higher than the number of years lost to maternal and childhood malnutrition [5]. The 2004 report by the WHO identifies obesity as a primary risk factor for an elevated rate of deaths by chronic disease, especially in developing countries, in which limited access to health care may prevent diagnosis and therapeutic approaches at a stage of the disease when an effective treatment was still possible [6]. Scrutiny of standard diets in developed and developing countries highlights one common paradox: while high in calories delivery - as they are mainly composed of energy-dense nutrients like purified sugars or edible oils - these diets are scarce in, or lack altogether, complex carbohydrates, fibers, proteins and micronutrients [5]. Supporting this imbalance, epidemiological studies have observed, for example, the presence of anemia in obese individuals dues to dietary iron deficiency [7,8]. The paucity of micronutrients intake can contribute to the onset and progression of obesity and obesity-related complications by inhibiting the efficacy of hormones regulating satiety centers in the CNS, promoting inflammation, or through other not fully elucidated mechanisms.

Increased levels of basal inflammation are commonly observed under obesity conditions [9] and type 2 diabetes [10]. Zinc deficiency has been associated iin a cause-effect relation with the enhanced basal levels of inflammation due to the increased translocation of NFkB to the nucleus of monocytes and other inflammation-responsive cells under conditions in which cellular zinc content is below the ideal level [9]. How exactly low zinc levels translate into an increased nuclear translocation of NFkB is not fully elucidated. Nevertheless, it is evident that the increased translocation of the transcription factor upregulates pro-inflammatory cytokine production [9], especially TNF-α and IL-6, which - in turn - exert autocrine and paracrine effects amplifying the intensity of the inflammatory process and its duration.

The role of zinc in diabetes, instead, is best explained by the role this cation plays in stabilizing insulin molecules within the secretory granules prior to their release by β-cells into the circulation [10]. Under zinc-deficiency conditions, insulin packaged into secretory granules becomes unstable and degrades more rapidly, thus limiting the half-life of the hormone and its effectiveness in peripheral tissues and contributing, together with the higher levels of basal inflammation, to the onset of peripheral insulin resistance[10]. In the case of the liver, the first organ to clear insulin from the circulation upon its release from pancreatic β-islets, reduced stimulatory effectiveness at the level of the hepatic insulin receptors alters glycemic homeostasis through a combination of reduced glycogen synthesis and increased gluconeogenesis [10]. Insulin is also less effective at down-regulating fatty acid metabolism in both liver and adipose tissue, which translates into increased lipolysis, hyper-triglyceridemia, and hyper-cholesterolemia [10]. The ensuing lipotoxicity [11] further compromises insulin responsiveness in peripheral tissues including skeletal muscles [11], with consequent negative impact on glycemic control.

Magnesium deficiency has also been associated with increased predisposition to diabetes [12] and inflammation [13]. The decreased effectiveness in insulin signaling under magnesium deficient conditions has been explained with decreased phosphorylation of insulin receptor substrate-1 (IRS1) in skeletal muscles, liver, and other tissues [12,14]. Also in the case of magnesium deficiency the increased basal level of inflammation has been explained with enhanced NFkB translocation to the nucleus and consequent production of pro-inflammatory cytokines [13,14]. Presently, it is undefined whether zinc and magnesium deficiency affect each other, and contribute to the pathophysiological alterations observed in obese and diabetic patients.

Additional examples of the importance of micronutrients are provided by the importance of selenium and glutathione levels as antioxidants[15], iron as an anti-anemic agent [7,8], and iodine for thyroid hormone synthesis and control of basal metabolism [16], just to name a few others.

Dietary Fat Intake

While some of the changes implemented in the US diet in the last three decades have certainly been beneficial, other equally desirable changes have not been implemented, or at least not to the same extent. For example, the consumption of the omega-3 fatty acids DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid), both abundantly present in fish such as salmon or herring, has remained low and steady. In contrast, the dietary intake of saturated and unsaturated fats, both associated with high risk of heart disease through increased LDL ('bad' cholesterol) and decreased HDL ('good' cholesterol) levels have remained largely unchanged. Saturated fats are present in meat, full-fat dairy products and some oils (e.g. coconut and palm) whereas unsaturated (trans) fats are present in various pre-packaged food items including cookies, pies, and frozen pizzas. The amount of trans fat in food has decreased in recent years as a result of the 2006 FDA mandate requiring their content to be listed in the food's nutritional

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label. Yet, pre-packaged products that provide less than 0.5 grams per serving can indicate 'no trans fats' content on the label without infringing such a mandate. A recent survey by Honors and colleagues [17] indicates that despite a ~30% decrease in the intake of trans fats in the Minnesota-St Paul area for the period 1980 – 2009, the daily intake of trans fats in the surveyed areas still accounts for ~1.9% of the daily caloric intake for men and 1.7% for women at front of the AHA recommended limit to be ≤1% (~2 g) [17]. The consumption of saturated fats in the same surveyed areas has also decreased, but it is still ranging at ~11% of the daily caloric intake *versus* a 5-6% AHA recommended limit [17]. In contrast, the consumption of the beneficial DHA and EPA omega-3-fatty acids has remained steady at ~80 mg and ~40 mg, respectively, *versus* a total recommended intake of 250mg/day [17].

Protein Intake and the 'Leverage' hypothesis

A second main paradox common to many diets is that while the intake of carbohydrates (low-carb diet), fatty acid (low-fat diet), or cholesterol (TLC or therapeutic lifestyle changes diet) have been restricted to a varying extent based on individual diets, the progressive reduction in dietary protein intake has not addressed in an effective and consistent manner. This has prompted several nutritionists and dieticians to propose the 'protein leverage' hypothesis whereby excess food consumption and associated weight gain directly relates to reduced dietary protein content [18]. Based upon the FAOSTAT database, from 1960 to 2000 the amount of energy derived from dietary carbohydrates and fat have both increased by 40% whereas the energy intake derived from proteins has remained essentially unchanged. The same database also shows a positive correlation between decline in protein intake and increase in the incidence of obesity for the period 1970 to 2000 [19]. In proposing the protein leverage hypothesis, Simpson and Raubenheimer have predicted that when the dietary protein content decreases below 14% obesity increases at a rate that is directly proportional to the percentage reduction in protein content [18].

Additional considerations

A nutritional aspect that has not been thoroughly elucidated in its implications is the propensity to obesity and related complications to manifest and recur within families or closed social enclaves. This despite the fact that maternal obesity has been consistently indicated as a predictor for the development of obesity in children [5]. Presently, it is unclear whether this diathesis depends on genetic transmission and/or prolonged exposure to a diet unbalanced in micro- and macro-nutrients. Imbalanced diets result in stunting during childhood, a condition that has been associated with the propensity for these children to become obese and develop diabetes later in life [5]. It is possible that early stunting - even when recovered - induces long-lasting hormonal and metabolic modifications that predispose to the onset of obesity at a later time. On the other hand, it cannot be excluded that persistent exposure to an imbalanced diet within a family cloister can contribute to the development of the mentioned pathologies later in life. In this contest, a puzzling aspect remains the observation that within a closed family cloister women show a higher incidence of obesity than their male counterpart despite being exposed to a seemingly similar diet.

Conclusions

The examples of dietary deficiency reported above indicate that selective micro- and macro-nutrient malnutrition conditions are associated with specific physio-pathological consequences including stunting, impaired cognitive development, and increased morbidity in children as well as in mothers. Other more severe consequences later in life include cancer, diabetes, atherosclerosis, hypertension, coronary heart disease, and stroke. Because of these consequences, restoration of deficient micro- and macro-nutrients in the diet has been attempted. It is important to note that studies focusing on a single micro- or macro-nutrient have provided inconsistent results, whereas diets providing a more ample supply of various micro-nutrients (e.g. diets enriched in fruit, vegetables, and whole grains) appeared to be more beneficial in reducing the risk for cardiovascular diseases, diabetes and cancer. Hence, emphasis is placed on the importance of interactive processes among various micro- and macro-nutrients over a single micro- or macro-nutrient enrichment.

Considered all together, these lines of evidence highlight the necessity for a better understanding of the importance of various nutrients and minerals for specific physiological and metabolic processes, and the negative consequences associated with malnutrition and specific and/or cumulative deficiencies. This increase in knowledge has already generated several promising results: 1) schools across the Nation have been overhauling their cafeteria menus to provide pupils with more nutritionally healthy choices while limiting the access to carbonated drinks and pre-packaged foods; 2) the food pyramid has been revised to take into account the increased needs for a more balanced diet; 3) increased awareness about the direct correlation between sodium intake and hypertension has resulted in decreasing sodium content as preserving agent in various pre-packaged food items; and 4) the use of high fructose corn syrup as a sweetener in carbonated drinks, yogurts, and other food products has been reduced to a large extent. In the latter case, the change has been dictated by the increasing and overwhelming clinical and experimental evidence that ingestion of fructose in quantities in excess of 40 g/day rapidly overpowers the ability of our body to properly metabolize it, resulting in various dysmetabolic responses ranging from increased caloric intake to the inability of fructose to elicit a proper insulin response, therefore limiting the control exerted by this hormone on our sense of satiety in the central nervous system, to increased inflammation in liver and adipose tissue.

It is our hope and belief that as the general knowledge increases, the general population will be better educated about diet quality and balance, portion sizes, and the necessity of changes in lifestyle to counteract a preventable condition that has already reached epidemic proportions.

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