Diseases of Civilization – Cancer, Diabetes, Obesity and Acne – the Implication of Milk, IGF-1 and mTORC1

Victor Gabriel CLATICI a, Cristiana VOICU b, Catalina VOAIDES b, Anca ROSEANU c, Madalina ICRIVERZI c, Stefana JURCOANE b

a Dermalife Medical Centre, Bucharest, Romania
b UASVM Bucharest, Faculty of Biotechnologies, Bucharest, Romania
c Department of Ligand-Receptor Interaction, Institute of Biochemistry of the Romanian Academy, Bucharest, Romania

ABSTRACT

Nutrition and food are one of the most complex aspects of human lives, being influenced by biochemical, psychological, social and cultural factors. The Western diet is the prototype of modern dietary pattern and is mainly characterized by the intake of large amounts of red meat, dairy products, refined grains and sugar. Large amounts of scientific evidence positively correlate Western diet to acne, obesity, diabetes, heart disease and cancer, the so-called “diseases of civilization”. The pathophysiological common ground of all these pathologies is the IGF-1 and mTORC pathways, which will be discussed further in this paper.

Keywords: cancer, diabetes, obesity, acne, milk, IGF-1, mTORC1.

INTRODUCTION

Food is an important environmental factor that can also influence the human genome (1). The most common products which are found, often inseparable, in the Western diet are milk and sugar. Milk and dairy products are recommended by most nutritional societies as important protein sources and for their effects on calcium metabolism and bone mineralization (2).

Milk has remarkable characteristics, and by far, the most important of all is that milk is the only nutrient that has the ability to sustain postnatal growth in all mammals (3). Recently, milk has been identified to activate mTORC1 in the cells of the recipient, therefore inducing con-
trolled species-specific growth (15). As a consequence, milk is no longer regarded as “just food” but an important factor of mammalian evolution (3, 4).

Historically, milk consumption and signaling was limited to the nursing period of different mammals. The Neolithic Homo sapiens was the first to introduce milk into his food chain between 8000-10,000 years ago (5, 6). Nowadays, milk and dairy products are important elements in the Western society’s diet, consumed by children and adults well after the age of weaning (2).

New emerging data highlight the negative effects of the Western lifestyle (stress, sedentari-ness and imbalanced diet) on health and its profound implications on disease states, compared to various populations living natural (7-9).

The main characteristics of the Western diet are a high glycemic load, increased intake of animal proteins and milk and its derivates, all of these being known to overstimulate mammalian target of rapamycin complex 1 (mTORC1) (10). The state of increased activation of (mTORC1) has been linked to obesity, T2DM, metabolic syndrome, cancer, neurodegenerative diseases and early aging (11-17).

Milk contains high amounts of growth-stimu-lating hormones, such as IGF-1, whose concen-trations have been shown to remain high even after the milk is being processed (pasteurization, homogenization, and digestion) (18).

The amino acid sequences are the same for human and bovine IGF-1, therefore bovine IGF-1 can bind to the human IGF receptor (19). In addition, IGF-1 digestion in the gut is being protected by milk’s proteins, therefore the IGF remains active in the serum after milk consump-tion (2).

Milk is often consumed in association with whey protein-based products, and this combination elevates postprandial insulin levels and basal IGF-1 plasma levels (20).

Interestingly, the consumer’s serum IGF-1 lev-els are not augmented by the cow’s milk IGF-1 content itself, but by the hepatic IGF-1 production stimulation via amino acid transfer induced by the milk (4).

Despite their low glycaemic indexes (GI), both fermented and non-fermented milk pro-ducts induce three to six fold higher insulinaemic responses (21).
A major factor for hepatic IGF-1 synthesis is tryptophan, which is mainly found in α-lactalbmin, an abundant whey protein (33, 34).

Another important factor critically involved in mTORC1 activation is glutamine, because it promotes cellular leucine uptake (35), while also being a crucial precursor of the glutaminolysis pathway (36-38).

The fatty acid palmitate, which comprises approximately 32% of milk's triglycerides (39, 40) is also able to activate mTORC (41) and enhance its lysosomal translocation (41), in the same place where BCAAs activate mTORC1 (42, 43).

As a consequence, the typical Western diet, mainly consisting in combinations of milk proteins and high glycaemic index products, has an important stimulating effect on serum insulin and IGF-1 levels, therefore promoting mitogenesis and antiapoptosis (3). Moreover, milk also transfers an epigenetic signalling “software” to its consumer, under the form of microRNAs, which are transported to their target cells via extracellular secretory nanovesicles called exosomes (44).

ACNE AND WESTERN CIVILISATION

Acne has become an almost universal disease in Western societies, with prevalence rates of 79-95% in the adolescent population, 40-54% in individuals over 25 years of age and 3-12% in middle aged persons (45). Acne is currently considered an obvious result of imbalanced nutrition induced by Western diet, a well known factor that exaggerates insulin/IGF-1 signalling (23).

Even though acne is considered to be a dermatosis directly induced by the effects of androgen on the pilosebaceous follicle, its course is much more strongly correlated with GH and IGF-1, than plasma androgen levels (59).

The link between acne and diet is therefore strongly related to the Western lifestyle, characterized by increased consumption of hyperglycaemic carbohydrates and milk which are known to increase insulin levels, IGF-1 production and mTORC1 signalling, key elements of acne pathogenesis (23, 49).

Western diet could be regarded as a maximized Neolithic diet, characterized by increased consumption of hyperglycemic carbohydrates and dairy products, which are known to increase insulin levels, IGF-1 production and mTORC1 signalling, key elements of acne pathogenesis (23, 49).

In 1885, Bulkley, following an extensive dietary study which included 1500 patients with acne, was one of the first investigators who raised the suspicion regarding the link between milk consumption and acne (50).

More recently, Harvard epidemiologists Adebamowo et al (51-53) provided the first epidemiological evidence on the link between milk consumption and acne, after evaluating the data collected from the retrospective Nurses’ Health Study II and the prospective Growing-up Today Study.

Later on, other controlled clinical studies highlighted the correlation between dairy consumption and acne vulgaris (54-57), identifying milk, saturated and trans fat consumption and a hyperglycemic load as major factors inducing or aggravating acne vulgaris (58).

MILK CONSUMPTION, IGF-1 SERUM LEVELS AND ACNE

Acne has been found in non-Western societies (Inuits, Okinawan Islanders, Ache hunters-gatherers, Kitavan Islanders), whose populations continue to adhere to Paleolithic dietary conditions (45). In contrast, acne has evolved to an almost epidemic disease in Westernized societies, highlighting the tremendous role played by environmental factors in its pathogenesis (45).

The knowledge regarding the link between acne and diet has culminated with the discovery that increased intake of both hyperglycemic carbohydrates and milk is a major factor in mTORC1 activation (18, 46, 47).

Environmental factors seem to be the most important pillars in the development of acne in modernized societies, and the identification of these factors might be the key for acne treatment in Western populations (45, 48).

OVERACTIVATED MTORC1 IN ACNE VULGARIS

Acne is currently considered a member of mTORC1-driven metabolic diseases, a family which also comprises type 2 diabetes, obesity and cancer (45, 49). Acne, alongside with other
diseases of the civilized world, such as obesity, arterial hypertension, insulin resistance, type 2 diabetes mellitus, cancer, and Alzheimer’s disease (28, 63-66), is associated with increased insulin/IGF-1 signalling, induced by hyper-glycemic diets and increased consumption of dairy products (22, 23, 52, 53, 62). These diseases of civilization are considered to be an indicator of systemically exaggerated mTORC1 signalling, acne being the most visible of all due to its location on the skin.

**mTORC1**

The mTORC complex, comprised of mTORC1 and mTORC2, is a complex system that responds to various environmental stimuli in order to control diverse cellular processes (48).

mTORC1 is a well known promoter of cell growth and proliferation in response to anabolic processes (67). In addition, mTORC stimulates gene transcription and translation, ribosome biogenesis and insulin, protein and lipid synthesis, while suppressing autophagic mechanisms (68-73). The Western diet acts as a strong metabolic signal for *mammalian target of rapamycin complex 1* (mTORC1), through glucose (ATP/energy status of the cell), essential amino acids (predominantly leucine), growth factors (insulin, IGF-1, fibroblast growth factors (FGFs) (74).

mTORC activation requires the coexistence of five major pathways:

1. The presence of growth factors such as insulin and IGF-1 (69, 75-77);  
2. Sufficient cellular energy, provided by glucose and ATP (78, 79);  
3. The availability of amino acids, predominantly leucine, growth factors (insulin, IGF-1, fibroblast growth factors (FGFs) (74).  

**MILK AND mTORC1 ACTIVATION**

Milk Provides BCAAs Activating mTORC1 – Milk is an important source of essential BCAAs, especially leucine (27), which is a major activator of mTORC1 (80).

Milk Provides Glutamine Activating mTORC1 – Milk proteins contain 8.09 g of glutamine/100g, 70% more than beef, which contains 4.75 g glutamine/100g (81). Glutamine activates mTORC1 via glutaminolysis pathway and controls cellular leucine uptake via the L-type amino acid transporter (LAT) (82-84).

Milk Stimulates Incretin and Insulin Secretion – Despite relatively low glycemic indices of whole milk and skim milk, the *insulinemic index* is much higher, for whole cow milk and skim milk, respectively (85, 86). The whey protein fraction is the major insulinotropic protein fraction in cow milk (87), but whey-derived amino acids also exert insulinotropic effects on pancreatic cells (82, 88).

**mTORC1 and General Health**

Several studies have revealed the relationship between increased BMI, BCAA profile and insulin resistance (90). Elevated plasma concentrations of BCAAs (leucine, isoleucine, valine) have been proposed as markers for obesity and future insulin resistance in children and adolescents in the United States (91).

Human cancer research recognized mTOR activity as a common molecular defect present in the majority of human cancers (92) and consequently, the mTORC1 signalling pathway has become a major focus in current studies (93). Besides cancer, increased mTORC1 signalling has also been associated with obesity, type 2 diabetes (11, 94) and other diseases of the civilized world, such as arterial hypertension and Alzheimer’s disease (14, 28, 63-66).

Because of its location on the skin, acne is considered a visible indicator of systemically exaggerated mTORC1 signalling and a predictable marker for obesity, arterial hypertension, insulin resistance, type 2 diabetes mellitus, cancer, and Alzheimer’s disease (28, 63-66).

Moreover, increased serum insulin and IGF-1 levels are involved in the development of various
cancers (95-97), including most types of epithelial neoplasia (98, 99). Daily milk and dairy consumption during adolescence and adulthood has been related to higher risk of prostate cancer (100, 101).

MILK AND HEALTH / NEGATIVE IMPACT

Milk and psychosexual development: As mentioned above, western nutrition is associated with acne break-outs, but it is also an important inducer of precocious puberty. Studies have revealed the fact that adolescent females engaged in sports activities who also adopt a low glycemic index diet have a delay in menarche (102).

In 1835, the median age of menarche was 16 years of age, whereas in 1970, the onset of puberty has dropped at 12 years (103), possibly due to increased milk and milk protein consumption (104, 105). Interestingly, recent studies have related precocious puberty to an increased risk of type 2 diabetes, metabolic syndrome and obesity in adulthood (106-111).

A new human phenotype, “the milk giant”, has emerged as a consequence of the Western diet. The modern man phenotype is characterized by increased linear growth (112), increased BMI and obesity (113-115), juvenile-onset myopia (116), insulin resistance (117) and increased risk of type 2 diabetes and cancer (28, 63, 64, 118).

An important adverse environmental factor and promoter of most modern chronic diseases is milk protein consumption, because it induces post-prandial hyperinsulinaemia and permanently increased IGF-1 serum levels (2).

Secondarily, Insulin/IGF-1 signalling regulate fetal and linear growth and T-cell maturation in the thymus, while also being involved in acne pathogenesis, atherosclerosis, diabetes mellitus, obesity, cancer and neurodegenerative diseases (2).

Milk consumption and linear growth – Milk is the best source of calcium for bone growth and mineralization, therefore it is positively associated with the accelerated linear growth and body height observed in industrialized countries over the last centuries (119).

Milk consumption and obesity – Milk intake may also be a risk factor for obesity (120, 121), since IGF-1 is a key element required for the differentiation of pre-adipocytes into adipocytes (122, 123). Adolescent obesity is characterized by compensatory hyperinsulinaemia, which by chronically suppressing IGFBP-1, increases the bioavailability of free IGF-1 (124).

Milk, insulin, IGF-1 and cancer – As previously mentioned, IGF-1 is a known mitogenic hormone, involved in cell growth, differentiation and metabolism (125), therefore potentially promoting tumor development and growth (126) in the breast, prostate, gastro-intestinal tract and lungs (95).

Milk, IGF-1 and cardiovascular disease – 35 years ago, Popham et al suggested that milk consumption and mortality from ischemic heart disease could also be related (127), when a linear correlation between milk protein consumption and male mortality from coronary heart disease has been demonstrated (128).

IGF-1 signalling and neurodegenerative diseases – Aging is considered the major risk factor for the development of neurodegenerative disease (129). The insulin/IGF-1 signalling pathway is an important factor that regulates lifespan, aging and neurodegenerative disease (130, 131). Consequently, milk consumption, due to its effects on the insulin-IGF-1 pathway, can be considered a possible accelerator of neurodegenerative disorders.

Research revealed that circulating IGF-1 can penetrate the blood-brain barrier and suggested the possibility that reduced IGF-1 signalling in the brain can lead to an extended mammalian life span (131).

CONCLUSIONS

Milk consumption has well established health benefits such as increased bone mineral content, reduced risk of protein-deficiency malnutrition and rickets and protects against dental caries and fractures (132-137).

Kapahi et al (138) coined the term “with TOR less is more”, which summarizes the core of treatment and prevention for the majority of diet-induced inflammatory skin disease.

Nowadays, more than 2000 years after Hippocrates wrote “Let food be your medicine, and let medicine be your food,” his words seem more truthful then ever and action must be taken as soon as possible.
The most important nutritional challenge for the future will be the attenuation of whey protein-based insulinoactive mechanisms, which requires an interdisciplinary cooperation between medicine, nutrition research and milk processing biotechnology.

Acne, the mirror of Western diet, can be regarded as a useful indicator of appropriate or inappropriate human nutrition.

The future of nutrition research and development, with focus on the generation of milk products with an insulinemic index of less than 45, will have a huge beneficial impact on the prevention of Modern World’s chronic diseases, such as acne, obesity, diabetes, neurodegenerative diseases and cancer (2).

Acknowledgments: This research was supported by the project “Determination of the effects of processed food on the ruminant environment and the productive performance of ruminants”, contract no. A.D.E.R. 6.2.2./2015.

Conflicts of interest: none declared.

Financial support: This work was supported by the Ministry of Agriculture and Rural Development by grant no. A.D.E.R. 6.2.2./2015.

References


34. Harp JB, Goldstein S, Phillips LS.


126. Resnicoff M, Basega R. The role of insulin-like growth factor-I receptor in transformation and apoptosis. 

127. Popham RE, Schmidt W, Israel Y. Variation in mortality from ischemic heart disease in relation to alcohol and milk consumption. 


129. Amaducci L, Tesco G. Aging as a major risk for degenerative diseases of the central nervous system. 

130. Cohen E, Dillin A. The insulin paradox: aging, proteotoxicity and neurodegeneration. 


133. Nicklas TA. Calcium intake trends and health consequences from childhood through adulthood. 


135. Pacha J. Development of intestinal transport function in mammals. 
*Physiol Rev* 2000;80:1633-1667.


137. Vacher PY, Bestetti G, Blum JW. Insulin-like growth factor I absorption in the jejunum of neonatal calves. 