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REVIEW

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

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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 disscussed 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-

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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, sedentariness 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-stimulating hormones, such as IGF-1, whose concentrations 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 consumption (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 levels 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 products induce three to six fold higher insulinaemic responses (21). ❑

MILK, INSULIN AND INSULIN GROWTH FACTOR 1 (IGF 1)

Milk exerts its signaling mechanisms by inducing long-lasting increase in serum IGF-1 levels and postprandial fast upregulation of insulin secretion (22, 23).

Interestingly, milk and its derivates have been shown to increase IGF-1 levels more than other dietary protein sources (9–16). IGF-1 has mainly metabolic and proliferative functions, acting like a hormone with distinct metabolic effects and specific IGF-1 receptors, which are present in almost every cell in the human body. IGF-1 is the mediator of the growth stimulating activity of GH (2).

Serum IGF-1 is mainly produced by the liver, with more than 90% of the molecules being bound to IGF-binding protein-3 (IGFBP-3) (18). The synthesis of IGF-1 is subject of hormones, nutrition, age, sex and genetic variability.

IGF-1 is a strong mitogenic factor, promoting cell growth and proliferation and inhibiting apoptosis (24). Cell growth and proliferation is induced by the activation of the IGF-1 receptor (IGF1R) and the subsequent upregulation of the phosphoinositol-3-kinase (PI3K)–protein kinase B (AKT) signalling cascade (24).

The insulinotropic amino acids, residing predominantly in the whey fraction of soluble milk proteins, are the main factors responsible for the stimulation of insulin secretion, therefore exerting the strongest insulin tropic effects, and not the carbohydrate content of milk (3).

The glutamine and the essential branched-chain amino acids (BCAAs), such as leonine, isoleucine, and valine, promote mTORC1-mediated insulin synthesis and secretion in the pancreatic cells (3).

Thus, milk and dairy, which are enriched in essential BCAAs, inhance mTORC1 levels (25, 26). mTORC1 activation is also promoted by leucine, an insulinotropic amino acid found in milk proteins (4).

Interestingly, the highest amount of leucine is not found in animal protein sources (8%), but in whey proteins (14%) (27).

The development of insulin resistance and type 2 diabetes mellitus can be accurately predicted by the persistence of elevated BCAA levels (28-32).

A major factor for hepatic IGF-1 synthesis is tryptophan, which is mainly found in α-lactalbumin, 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).

Acne has not been found in non-Western societies (Inuits, Okinawan Islanders, Ache hunter-gatherers, Kitavan Islanders), whose populations continue the 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 nutrition 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).

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), indentifying 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

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 to plasma androgen levels (59). These alterations in IGF-1 serum levels have been identified especially in adult acne patients (60, 61).

The link between acne and diet is therefore strongly related to the Western lifestyle, characterized by increased consumption of hyperglycaemic carbohydrates as well as insulinotropic milk and dairy products, which eventually lead to increased insulin secretion and insulin-like growth factor-1 (IGF-1) signalling (22, 45, 47, 62). ❑

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 essential BCAAs such as leucine (25, 69, 73, 74, 76, 77);

4) The presence of glutamine (35, 38), and

5) The availability of saturated fatty acids, especially palmitic acid (41). ❑

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/100 g, 70% more than beef, which contains 4.75 g glutamine/100g (81). Glutamine activates mTORC1 *via* glutaminolysis pathway and controles 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).

Milk Stimulates IGF-1 Secretion Activating mTORC1 – Extended research confirmed that a diet rich in milk increases serum levels of insulin-like growth factor-1 (IGF-1) (89).

Milk Provides Palmitic Acid Activating mTORC1 – The amount of lipids in bovine milk ranges form 3.5 to 5%, with almost 98% of them being composed triacylglycerols (39). The major fatty acid of milk lipids is palmitate (C16:0) (39, 40), which activates mTORC1 at the lysosomal compartment, similarly to BCAAs (41).

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 insulinotropic 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). ❑

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REFERENCES

1. **Landecker H.** Food as exposure: nutritional epigenetics and the new metabolism. *Biosocieties* 2011;2:167-194.
2. **Melnik BC.** Milk – The promoter of chronic Western diseases. *Med Hypotheses* 2009. doi:10.1016/ j.mehy.2009.01.008
3. **Melnik BC.** The Pathogenic Role of Persistent Milk Signaling in mTORC1- and Milk-MicroRNA-Driven Type 2 Diabetes Mellitus. *Current Diabetes Reviews* 2015;11:46-62.
4. **Melnik BC, John SM, Schmitz G.** Milk is not just food but most likely a genetic transfection system activating mTORC1 signaling for postnatal growth. *Nutr J* 2013;12:103.
5. **Dunne J, Evershed RP, Salque M, et al.** First dairying in green Saharan Africa in the fifth millennium BC. *Nature* 2012;486:390-394.
6. **Curry A.** Archaeology: The milk revolution. *Nature* 2013;500:20-22.
7. **Melnik B.** Milk consumption: aggravating factor of acne and promoter of chronic diseases of Western societies. *J Dtsch Dermatol Ges* 2009;7:364-370.
8. **Duvnjak L, Duvnjak M.** The metabolic syndrome—an ongoing story. *J Physiol Pharmacol* 2009;60;Suppl 7:19-24.
9. **Berra B, Rizzo AM.** Glycemic index, glycemic load: new evidence for a link with acne. *J Am Coll Nutr* 2009;28;Suppl:450S-4S.
10. **Melnik BC, John SM, Plewig G.** Acne: Risk indicator for increased body mass index and insulin resistance. *Acta Derm Venereol* 2013;93:644-649.
11. **Zoncu R, Efeyan A, Sabatini DM.** mTOR: from growth signal integration to cancer, diabetes and ageing. *Nature Rev Mol Cell Biol* 2011;12:21-35.
12. **Johnson SC, Rabinovitch PS, Kaeberlein M.** mTOR is a key modulator of ageing and age-related disease. *Nature* 2013;493:338-345.
13. **Cornu M, Albert V, Hall MN.** mTOR in aging, metabolism, and cancer. *Curr Opin Genet Dev* 2013;23:53-62.
14. **Oddo S.** The role of mTOR signaling in Alzheimer disease. *Front Biosci* 2012;S4:941-952.
15. **Tang Z, Bereczki E, Zhang H, et al.** Mammalian target of rapamycin (mTor) mediates tau protein dyshomeostasis: implication for Alzheimer disease. *J Biol Chem* 2013;288:15556-15570.
16. **Mendelsohn AR, Larrick JW.** Dissecting mammalian target of rapamycin to promote longevity. *Rejuvenation Res* 2012;15:334-337.
17. **Xu S, Cai Y, Wei Y.** mTOR signaling from cellular senescence to organismal aging. *Aging Dis* 2014;5:263-273.
18. **Melnik BC, Schmitz G.** Role of insulin, insulin-like growth factor-1, hyperglycemic food and milk consumption in the pathogenesis of acne vulgaris. *Exp Dermatol* 2009;10:833-841.
19. **Francis GL, Upton FM, Ballard FJ, McNeil KA, Wallace JC.** Insulin-like growth factors 1 and 2 in bovine colostrum. Sequences and biological activities compared with those of a potent truncated form. *Biochem J* 1988;251:95-103.
20. **Melnik BC.** FoxO1 – the key for the pathogenesis and therapy of acne? *J Dtsch Dermatol Ges* 2010;8:105–113.
21. **Östman EM, Liljeberg Elmstahl HGM, Björck IME**. Inconsistency between glycemic and insulinemic responses to regular and fermented milk products. *Am J Clin Nutr* 2001;74:96-100.
22. **Melnik BC.** Evidence for acne-promoting effects of milk and other insulinotropic dairy products. *Nestle Nutr Workshop Ser Pediatr Program* 2011;67:131-145.
23. **Melnik BC, John SM, Schmitz G.** Over-stimulation of insulin/IGF-1 signaling by Western diet may promote diseases of civilization: lessons learnt from Laron syndrome. *Nutr Metab (Lond)* 2011;8:41.
24. **Denley A, Cosgrove LJ, Booker GW, Wallace JC, Forbes BE.** Molecular interactions of the IGF system. *Cytokine Growth Factor Rev* 2005;16:421-439.
25. **Kim J, Guan KL.** Amino acid signaling in TOR activation. *Annu Rev Biochem* 2011;80:1001-1032.
26. **Liao XH, Majithia A, Huang X, et al.** Growth control via TOR kinase signaling, an intracellular sensor of amino acid and energy availability, with crosstalk potential to proline metabolism. *Amino Acids* 2008;35:761-770.
27. **Millward DJ, Layman DK, Tomé D, Schaafsma G**. Protein quality assessment: impact of expanding understanding of protein and amino acid needs for optimal health. *Am J Clin Nutr* 2008;5:1576S-1581S.
28. **Melnik BC.** Leucine signaling in the pathogenesis of type 2 diabetes and obesity. *World J Diabetes* 2012;3:38-53.
29. **Melnik BC.** The pathogenic role of persistent milk signaling in mTORC1- and milk-microRNA-driven type 2 diabetes mellitus. *Curr Diabetes Rev* 2015;11:46-62.
30. **Giesbertz P, Daniel H.** Branched-chain amino acids as biomarkers in diabetes. *Curr Opin Clin Nutr Metab Care* 2016;19:48-54.
31. **Zhao X, Han Q, Liu Y, et al.** The relationship between branched-chain amino acid related metabolomic signature and insulin resistance: A systematic review. *J Diabetes Res* 2016;2016:2794591.
32. **Yoon MS.** The emerging role of branched-chain amino acids in insulin resistance and metabolism. *Nutrients* 2016;8. pii: E405.
33. **Heine W, Radke M, Wutzke KD, Peters E, Kundt G.** Alpha-lactalbumin enriched low-protein infant formulas: a comparison to breast milk feeding. *Acta Paediatr* 1996;9:1024-1028.
34. **Harp JB, Goldstein S, Phillips LS.**

Nutrition and somatomedin. XXIII. Molecular regulation of IGF-I by amino acid availability in cultured hepatocytes. *Diabetes* 1991;1:95-101.
35. **Nicklin P, Bergman P, Zhang B, et al.** Bidirectional transport of amino acids regulates mTOR and autophagy. *Cell* 2009;3:521-534.
36. **Jewell JL, Kim YC, Russell RC, et al.** Metabolism. Differential regulation of mTORC1 by leucine and glutamine. *Science* 2015;6218:194-198.
37. **Averous J, Lambert-Langlais S, Carraro V, et al.** Requirement for lysosomal localization of mTOR for its activation differs between leucine and other amino acids. *Cell Signal* 2014;9:1918-1927.
38. **Duran RV, Oppliger W, Robitaille AM, et al.** Glutaminolysis activates Rag-mTORC1 signaling. *Mol Cell* 2012;3:349-358.
39. **Jensen RG, Ferris AM, Lammi-Keefe CJ.** The composition of milk fat. *J Dairy Sci* 1991;9:3228-3243.
40. **Bitman J, Wood DL.** Changes in milk fat phospholipids during lactation. *J Dairy Sci* 1990;5:1208-1216.
41. **Yasuda M, Tanaka Y, Kume S, et al.** Fatty acids are novel nutrient factors to regulate mTORC1 lysosomal localization and apoptosis in podocytes. *Biochim Biophys Acta* 1842;2014:1097-10108.
42. **Zheng L, Zhang W, Zhou Y, et al.** Recent advances in understanding amino acid sensing mechanisms that regulate mTORC1. *Int J Mol Sci* 2016;17. pii: E1636.
43. **Manifava M, Smith M, Rotondo S, et al.** Dynamics of mTORC1 activation in response to amino acids. *Elife* 2016;5. pii: e19960.
44. **Melnik BC, Kakulas F, Geddes DT, et al.** Milk miRNAs: Simple nutrients or systemic functional regulators? *Nutr Metab (Lond)* 2016;13:42.
45. **Cordain L, Lindeberg S, Hurtado M, Hill K, Eaton SB, Brand-Miller J.** Acne vulgaris. A disease of Western civilization. *Arch Dermatol* 2002;138:1584-1590.
46. **Melnik BC, Zouboulis CC.** Potential role of FoxO1 and mTORC1 in the pathogenesis of Western diet-induced acne. *Exp Dermatol* 2013;22: 311-315.
47. **Melnik BC.** Diet in acne: further evidence for the role of nutrient signalling in acne pathogenesis. *Acta Derm Venereol* 2012;92:228-231.
48. **Melnik BC.** Acne vulgaris: The metabolic syndrome of the pilosebaceous follicle. *Clinics in Dermatology* 2018;36:29-40.
49. **Melnik B.** Dietary intervention in acne: Attenuation of increased mTORC1 signaling promoted by Western diet. *Dermatoendocrinology* 2012;4:20-32.
50. **Bulkley LD.** In: *Acne, its Etiology, Pathology and Treatment.* New York, NY: GP Putnam's Sons, 1885.
51. **Adebamowo CA, Spiegelman D, Danby FW, Frazier AL, Willett WC, Holmes MD.** High school dietary dairy intake and teenage acne. *J Am Acad Dermatol* 2005;2:207-214.
52. **Adebamowo CA, Spiegelman D, Berkey CS, et al.** Milk consumption and acne in adolescent girls. *Dermatol Online J* 2006;124:1.
53. **Adebamowo CA, Spiegelman D, Berkey CS, et al.** Milk consumption and acne in teenaged boys. *J Am Acad Dermatol* 2008;5:787793.
54. **Di Landro A, Cazzaniga S, Parazzini F, et al.** Family history, body mass index, selected dietary factors, menstrual history, and risk of moderate to severe acne in adolescents and young adults. *J Am Acad Dermatol* 2012;67:1129-1135.
55. **Ismail NH, Manaf ZA, Azizan NZ.** High glycemic load diet, milk and ice cream consumption are related to acne vulgaris in Malaysian young adults: A case control study. *BMC Dermatol* 2012;12:13.
56. **LaRosa CL, Quach KA, Koons K, et al.** Consumption of dairy in teenagers with and without acne. *J Am Acad Dermatol* 2016;75:318-322.
57. **Ulvestad M, Bjertness E, Dalgard F, et al.** Acne and dairy products in ad- olescence: Results from a Norwegian longitudinal study. *J Eur Acad Dermatol Venereol* 2017;31:530-535.
58. **Burris J, Rietkerk W, Woolf K.** Relationships of self-reported dietary factors and perceived acne severity in a cohort of New York young adults. *J Acad Nutr Diet* 2014;114:384-392.
59. **Cara JF, Rosenfield RL, Furlanetto RW.** A longitudinal study of the relationship of plasma somatomedin-C concentration to the pubertal growth spurt. *Am J Dis Child* 1987;141:562-564.
60. **Aizawa H, Niimura M.** Elevated serum insulin-like growth factor-1 (IGF-1) levels in women with post-adolescent acne. *J Dermatol* 1995;22:249-252.
61. **Cappel M, Mauger D, Thiboutot D.** Correlation between serum levels of insulin-like growth factor-1, dehydroepiandrosterone sulfate, and dihydrotestosterone and acne lesion counts in adult women. *Arch Dermatol* 2005;141:333-338.
62. **Smith RN, Mann NJ, Braue A, Mäkeläinen H, Varigos GA.** The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. *J Am Acad* Dermatol 2007;57:247-256.
63. **Proud CG.** mTOR signalling in health and disease. *Biochem Soc Trans* 2011;39:431-436.
64. **Melnik BC.** Excessive leucine-mTORC1-signalling of cow milk-based infant formula: the missing link to understand early childhood obesity. *J Obes* 2012;D197653.
65. **Harlan SM, Guo DF, Morgan DA, Fernandes-Santos C, Rahmouni K.** Hypothalamic mTORC1 signalling controls sympathetic nerve activity and arterial pressure and mediates leptin effects. *Cell Metab* 2013;17:599-606.
66. **Pópulo H, Lopes JM, Soares P.** The mTOR signalling pat- hway in human cancer. *Int J Mol Sci* 2012; 13: 1886-1918.
67. **Howell JJ, Ricoult SJ, Ben-Sahra I, et al.** A growing role for mTOR in promoting anabolic metabolism. *Biochem Soc Trans* 2013;41:906-912.
68. **Wang X, Proud CG.** Nutrient control of TORC1, a cell-cycle regulator. *Cell* 2009;19:260-267.
69. **Sengupta S, Peterson TR, Sabatini DM.** Regulation of the mTOR complex 1 pathway by nutrients, growth factors, and stress. *Mol Cell* 2010;40:310-322. doi: 10.1016/j.molcel.2010.09.026.
70. **Suzuki T, Inoki K.** Spatial regulation of the mTORC1 system in amino acids sensing pathway. *Acta Biochim Biophys Sin* 2011;43:671-679. doi: 10.1093/abbs/gmr066.
71. **Wang X, Proud CG.** mTORC1 signaling: what we still don´t know. *J Mol Cell Biol* 2011;3:206-220. doi: 10.1093/jmcb/mjq038.
72. **Shaw RJ.** LKB1 and AMPK control of mTOR signalling and growth. *Acta Physiol* (Oxf.) 2009;196:65-80. doi: 10.1111/j.1748-1716.2009.01972.x.
73. **Avruch J, Long X, Ortiz-Vega S, Rapley J, Papageorgiou A, Dai N.** Amino acid regulation of TOR complex 1. *Am J Physiol Endocrinol Metab* 2009;296:592-602. doi: 10.1152/ajpendo.90645.2008.
74. **Inoki K, Ouyang H, Li Y, Guan KL.** Signaling by target of rapamycin proteins in cell growth control. *Microbiol Mol Biol Rev* 2005;69:79-100.
75. **Foster KG, Fingar DC.** Mammalian target of rapamycin (mTOR): conducting the cellular signaling symphony. *J Biol Chem* 2010;285:14071-1477.
76. **Laplante M, Sabatini DM.** mTOR signaling. *Cold Spring Harb Perspect Biol* 2012; 4:pii: a011593.
77. **Efeyan A, Sabatini DM.** Nutrients and growth factors in mTORC1 activation. *Biochem Soc Trans* 2013;41:902-905.
78. **Xu J, Ji J, Yan XH.** Cross-talk between AMPK and mTOR in regu- lating energy balance. *Crit Rev Food Sci Nutr* 2012;52:373-381.
79. **Shaw RJ, Kosmatka M, Bardeesy N, et al.** The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress. *Proc Natl Acad Sci USA* 2004;101:3329-3335.
80. **Dodd KM, Tee AR.** Leucine and mTORC1: a complex relationship. *Am J Physiol Endocrinol Metab* 2012;302:E1329-42.
81. **Lenders CM, Liu S, Wilmore DW, et al.** Evaluation of a novel food composition database that includes glutamine and other amino acids derived from gene sequencing data. *Eur J Clin Nutr* 2009;63:1433-1439.
82. **McDaniel ML, Marshall CA, Pappan KL, Kwon G.** Metabolic and autocrineregulation of the mammalian

target of rapamycin by pancreatic cells. *Diabetes* 2002;51:2877-2885.
83. **Lorin S, Tol MJ, Bauvy C, et al.** Glutamate dehydrogenase contributes to leucine sensing in the regulation of autophagy. *Autophagy* 2013;9:850-860.
84. **Xu G, Kwon G, Cruz WS, Marshall CA, McDaniel ML.** Metabolic regulation by leucine of translation initiation through the mTOR signaling pathway by pancreatic beta-cells. *Diabetes* 2001;50:353-360.
85. **Holt S, Brand Miller J, Petocz P.** An insulin index of foods. The insulin demand generated by 1000-kK portions of common foods. *Am J Clin Nutr* 1997;66:1264-1276.
86. **Hoyt G, Hickey MS, Cordain L.** Dissociation of the glycaemic and insulinaemic responses to whole and skimmed milk. *Br J Nutr* 2005;93:175-177.
87. **Hoppe C, Mølgaard C, Dalum C, Vaag A, Michaelsen KF.** Differential effects of casein versus whey on fasting plasma levels of insulin, IGF-1 and IGF-1/ IGFBP-3: results from a randomized 7-day supplementation study in prepubertal boys. *Eur J Clin Nutr* 2009;63:1076-1083.
88. **Yang J, Chi Y, Burkhardt BR, Guan Y, Wolf BA.** Leucine metabolism in regulation of insulin secretion from pancreatic beta cells. *Nutr Rev* 2010;68:270-279.
89. **Qin LQ, He K, Xu JY.** Milk consumption and circulating insulin- like growth factor-I level: a systematic literature review. *Int J Food Sci Nutr* 2009;60:330-340.
90. **Morris C, O Grada C, Ryan M, Roche HM, Gibney MJ, Gibney ER, Brennan L.** The relationship between BMI and metabolomics profiles: a focus on amino acids. *Proceed Nutr Soc* 2012;71:634-638.
91. **McCormack SE, Shaham O, McCarthy MA, Deik AA, Wang TJ, Gerszten RE, et al.** Circulating branched-chain amino acid concentrations are associated with obesity and future insulin resistance in children and adolescents. *Pediatr Obes* 2012;8:52-61.
92. **Menon S, Manning BD.** Common corruption of the mTOR signaling network in human tumors. *Oncogene* 2009;27:S43-S51. [PubMed: 19956179]
93. **Bhaskar PT, Hay N.** The two TORCs and Akt. *Develop Cell*. 2007;12:487–502. doi: 10.1016/j.devcel.2007.03.020.
94. **Shaw RJ, Cantley LC.** Ras, PI(3)K and mTOR signalling controls tumour cell growth. *Nature* 2006; 441: 424-430.
95. **Furstenberger G, Senn H-J.** Insulin-like growth factors and cancer. *Lancet* 2002;3:298–302.
96. **Boyd D B.** Insulin and cancer. *Integr Cancer Ther* 2003;2:315-329.
97. **Pollack MN.** Insulin, insulin-like growth factors, insulin resistance, and neoplasia. *Am J Clin Nutr* 2007;86:820-822.
98. **Clayton PE, Banerjee I, Murray PG, Renehan AG.** Growth hormone, the insulin- like growth factor axis, insulin and cancer risk. *Nat Rev Endocrinol* 2011;7:11-24.
99. **Pollak M.** Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer* 2008;8:915-928.
100. **Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Tjønneland A, et al.** Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer* 2008;98:1574-1581.
101. **Torfadottir JE, Steingrimsdottir L, Mucci L, Aspelund T, Kasperzyk JL, Olafsson O, et al.** Milk intake in early life and risk of advanced prostate cancer. *Am J Epidemiol* 2012;175:144-153.
102. **Frisch R, Wyshak G, Vicent L.** Delayed menarche and amenorrhea in ballet dancers. *N England J Med* 1980;303:17-19.
103. **Frisch R.** Weight at menarche: similarity for well- nourished and undernourished girls at differing ages, and evidence for historical constancy. *Pediatrics* 1972;50:445-450.
104. **Wiley AS.** Milk intake and total dairy consumption: associations with early menarche in NHANES 1999–2004. *PLoS One* 2011; 6: e14685.
105. **Lucky AW, Biro FM, Simbartl LA, Morrison JA, Sorg NW.** Predictors of severity of acne vulgaris in young adolescent girls: results of a five-year longitudinal study. *J Pediatr* 1997;130:30-39.
106. **Mendoza N, Galliano D, Salamanca A, Castro JE, Mozas J, Sánchez-Borrego R, et al.** Lowering the age at menarche and risk of early menarche in a population of Spanish postme- nopausal women during the past two decades. *Menopause Int* 2010;16:111-114.
107. **Chen L, Zhang C, Yeung E, Ye A, Mumford SL, Wactawski- Wende J, Schisterman EF.** Age at menarche and metabolic markers for type 2 diabetes in premenopausal women: the BioCycle Study. *J Clin Endocrinol Metab* 2011;96:E1007-E1012.
108. **Pierce MB, Kuh D, Hardy R.** The role of BMI across the life course in the relationship between age at menarche and diabetes, in a British Birth Cohort. *Diabet Med* 2012;29:600-603.
109. **Conway BN, Shu xO, Zhang X, Xiang YB, Cai H, Li H, et al.** Age at menarche, the leg length to sitting height ratio, and risk of diabetes in middle-aged and elderly Chinese men and women. *PLoS One* 2012;7:e30625.
110. **Dreyfus JG, Lutsey PL, Huxley R Pankow JS, Selvin E, Fernández-Rhodes L, et al.** Age at menarche and risk of type 2 diabetes among African-American and white women in the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia* 2012;55:2371-2380.
111. **Stöckl D, Meisinger C, Peters A Thorand B, Huth C, Heier M, et al.** Age at menarche and its association with the metabolic syndrome and its components: results from the KORA F4 study. *PLoS One* 2011;6:e26076.
112. **Hoppe C, Mølgaard C, Michaelsen KF.** Cow's milk and linear growth in industrialized and developing countries. *Annu Rev Nutr* 2006;26:131-173.
113. **Berkey CS, Rockett HH, Willett WC, Colditz GA.** Milk, dairy fat, dietary calcium, and weight gain. *Arch Pediatr Adolesc Med* 2005;159:543-550.
114. **Wiley AS.** Dairy and milk consumption and child growth: is BMI involved? An analysis of NHANES 1999–2004. *Am J Hum Biol* 2010;22:517-525.
115. **Arnberg K, Mølgaard C, Michaelsen KF, Jensen SM, Trolle E, Larnkjær A.** Skim milk, whey, and casein increase body weight and whey and casein increase the plasma C-peptide concentration in overweight adolescents. *J Nutr* 2012;142:2083-2090.
116. **Cordain L, Eaton SB, Brand Miller J, Lindeberg S, Jensen C.** An evolutionary analysis of the aetiology and pathogenesis of juvenile-onset myopia. *Acta Opthalmol Scand* 2002;80:125-135.
117. **Hoppe C, Molgaard C, Vaag A, Barkholt V, Michaelsen KF.** High intakes of milk, but not meat, increase s-insulin and insulin resistance in 8-year-old boys. *Eur J Clin Nutr* 2005;59:393-398.
118. **Melnik BC, John SM, Carrera-Bastos P, Cordain L.** The impact of cow's milk-mediated mTORC1-signaling in the initiation and progression of prostate cancer. *Nutr Metab (Lond)* 2012;9:74.
119. **Esterle L, Sabatier J-P, Metz FG, Walrant-Debray O, Guaydier-Souquières G, Jehan F, et al.** Milk, rather than other foods, is associated with vertebral bone mass and circulating IGF-1 in female adolescents. *Osteoporos Int* 2008; doi:10.1007/s00198-008-0708-x.
120. **Olsen SF, Halldorsson TI, Willett WC, Knudsen VK, Gilman MW, Mikkelsen TB, et al.** Milk consumption during pregnancy is associated with increased infant size at birth: prospective cohort study. *Am J Clin Nut*r 2007;86:1104-1110.
121. **Sorensen HT, Sabroe S, Rothman KJ, Gillman M, Fischer P, Sorensen TI.** Relation between weight and length at birth and body mass index in young adulthood: corhort study. *BMJ* 1997;315:1137.
122. **Ailhaud G, Grimaldi P, Negrel R.** A molecular view of adipose tissue. *Int J Obes* 1992;16(Suppl. 2):S17–21.
123. **Blüher S, Kratzsch J, Kiess W.** Insulin-like growth factor-I, growth hormone and insulin in white adipose tissue. *Best Pract Res Clin Endocrinol Metab* 2005;19:577-587.
124. **Attia N, Tamborlane WV, Heptulla R, Maggs D, Grozman A, Sherwin RS, et al.** The metabolic syndrome and insulin-like growth factor-I regulation in adolescent obesity. *J Clin Endocrinol Metab* 1998;83:1467-1471.
125. **Le Roith D.** Insulin-like growth factors. *New Engl J Med* 1997;336:633-640.

126. **Resnicoff M, Basega R.** The role of insulin-like growth factor-I receptor in transformation and apoptosis. *Ann NY Acad Sci* 1998;842:76-81.
127. **Popham RE, Schmidt W, Israel Y.** Variation in mortality from ischemic heart disease in relation to alcohol and milk consumption. *Med Hypotheses* 1983;12:321-329.
128. **Seely S.** Diet and coronary disease: a survey of mortality rates and food consumption statistics of 24 countries. *Med Hypotheses* 1981;7:907-918.
129. **Amaducci L, Tesco G.** Aging as a major risk for degenerative diseases of the central nervous system. *Curr Opin Neurol* 1994;7:283-286.
130. **Cohen E, Dillin A.** The insulin paradox: aging, proteotoxicity and neurodegeneration. *Nat Rev Neurosci* 2008;9:759-767.
131. **Taguchi A, White MF.** Insulin-like signaling, nutrient homeostasis, and life span. *Ann Rev Physiol* 2008;70:191-212.
132. **Kalkwarf HJ, Khoury JC, Lanphear BP.** Milk intake during childhood and adolescence, adult bone density, and osteoporotic fractures in US women. *Am J Clin Nutr* 2003;77:257-265.
133. **Nicklas TA.** Calcium intake trends and health consequences from childhood through adulthood. *J Am Coll Nutr* 2003;22:340-356.
134. **Philipps AF, Kling PJ, Grille JG, Dvorak B.** Intestinal transport of insulin-like growth factor-I (igf-I) in the suckling rat. *J Pediatr Gastroenterol Nutr* 2002;35:539-544. doi: 10.1097/00005176-200210000-00015.
135. **Pacha J.** Development of intestinal transport function in mammals. *Physiol Rev* 2000;80:1633–1667.
136. **Rao RK, Lam K, Philipps AF, Williams C, Lake M, Koldovsky O.** Presence of multiple forms of peptidase inhibitors in rat milk. *J Pediatr Gastroenterol Nutr* 1993;17:414-420.
137. **Vacher PY, Bestetti G, Blum JW.** Insulin-like growth factor I absorption in the jejunum of neonatal calves. *Biol Neonate* 1995;68:354-367.
138. **Kapahi P, Chen D, Rogers AN, et al.** With TOR, less is more: a key role for the conserved nutrient-sensing TOR pathway in aging. *Cell Metab* 2010;6:453-465.