MINI-REVIEW

Acne: Risk Indicator for Increased Body Mass Index and Insulin Resistance

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Acne appears to represent a visible indicator disease of over-activated mammalian target of rapamycin complex 1 (mTORC1) signalling, an unfavourable metabolic deviation on the road to serious common Western diseases of civilisation associated with increased body mass index and insulin resistance. Exaggerated mTORC1 signalling by Western diet explains the association of acne with increased body mass index, insulin resistance, and early onset of menarche. Both, a high glycaemic load and increased consumption of milk and milk products, staples of Western diet, aggravate mTORC1 signalling. This review of the literature summarises present evidence for an association between acne, increased body mass index, insulin resistance and Western diet. By dietary intervention with a Palaeolithic-type diet, the dermatologist has the chance to attenuate patients' increased mTORC1 signalling by reducing glycaemic load and milk consumption, which may not only improve acne but may delay the march to more serious mTORC1-driven diseases of civilisation. *Key words: acne, body mass index, glycaemic load, insulin resistance, milk consumption, mTORC1.*

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Kwon et al. (1) recently demonstrated in this journal that a low glycaemic load (GL) diet had beneficial effects in the treatment of acne. High GL is a characteristic feature of Western diet, which is frequently associated with increased body mass index (BMI) and increased body fat composition. Dietary glycaemic index (GI) and GL were positively associated with body fatness among Danish boys aged 16 years (2). These observations already point to an association between acne and increased BMI. Accumulating evidence underlines the role of Western diet in the pathogenesis of acne. Two major compounds of Western diet have been identified to drive acne pathogenesis: (*i*) hyperglycaemic carbohydrates (high GL) and (*ii*) insulinotropic milk/dairy products, both promoting increased insulin/

insulin-like growth factor-1 (IGF-1) signalling (3–6). High BMI is obviously the clinical correlate of a high anabolic state of metabolism. The first epidemiological evidence for an association between milk consumption and acne has been presented by the retrospective evaluation of 47,355 US women participating in the Nurses' Health Study II (NHSII) (7). Two following prospective epidemiological studies confirmed the milk-acne relationship in the Growing Up Today Study with 6,094 girls (8) and 4,273 boys (9), who are the offspring of the mothers of the NHSII.

THE RELATIONSHIP BETWEEN ACNE AND INCREASED BODY MASS INDEX

Intriguingly, Berkey et al. (10) followed 12,829 children of the Growing Up Today Study and found an association between milk consumption and weight gain expressed as an increase of body mass index (BMI). These results of the Growing Up Today Study pointing to a milk-acne and milk-BMI relationship thus imply the possibility of an acne-BMI relationship (Fig. 1). In fact, Di Landro et al. (11) have recently reported that acne risk was reduced in Italian adolescents and young adults with lower BMI. Accordingly, a lower BMI has been associated with lower acne prevalence in Taiwanese boys and girls (12). In contrast, Halvorsen et al. (13) observed an association between increased BMI and acne in female Norwegian adolescents. Furthermore, British male soldiers older than 20 years with acne have been reported to be heavier than those with-
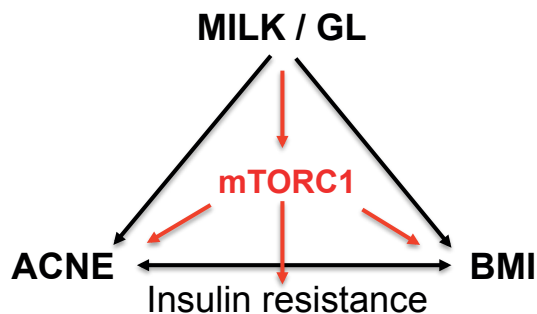

Fig. 1. Relationship between high milk consumption/high glycaemic load (GL) and acne as well as increased body mass index (BMI). High GL and milk activate mammalian target of rapamycin complex 1 signalling.

out acne (14). Del Prete et al. (15) recently provided evidence that young Italian males affected with acne had a high BMI and exhibited insulin resistance. Thus, substantial worldwide evidence appears to support an acne-BMI relationship (11–15). High BMI is a major factor of the metabolic syndrome, which is associated with insulin resistance and represents the typical feature of metabolic diseases of Western civilisation. Indeed, Cordain et al. (3) have suggested that acne belongs to the family of diseases of Western civilisation like obesity, type 2 diabetes mellitus and cancer.

mTORC1-ACTIVITY AND BODY MASS INDEX

At the cellular level, nutrient, amino acid as well as insulin-/IGF-1 availability are sensed by the nutrient-sensitive kinase mammalian target of rapamycin complex 1 (mTORC1), the central cellular regulator promoting protein and lipid synthesis, cell growth, and proliferation (16). From all amino acids, the branched-chain amino acid (BCAA) leucine plays a crucial role for mTORC1 activation (16, 17). Not by chance, milk provides highest amounts of leucine in comparison to all other animal proteins to optimise mTORC1 activation for postnatal growth. Several recent metabolomics studies underline the relationship between high plasma BCAA profiles, increased BMI and insulin resistance recently reviewed by Morris et al. (18). Thus, acne appears to develop in a metabolic environment with increased mTORC1 signalling and has been proposed to represent a visible mTORC1-driven disease of civilisation (19). In this regard, acne appears to feature over-stimulated mTORC1 signalling affecting the sebaceous follicle aggravated by nutrient signals derived from Western diet (6, 19).

MILK AND INCREASED BODY MASS INDEX

Milk has been identified as a promoter of mTORC1-mediated anabolic endocrine signalling created for the stimulation of postnatal growth in mammals (19). Thus, milk is not "just food" but functions as an endocrine relay system enhancing postnatal mTORC1 signalling comparable to enhanced IGF-1/mTORC1 signalling promoting pubertal growth (Fig. 2) (19). Milk protein consumption increases plasma levels of highly insulinotropic BCAAs (leucine, isoleucine and valine) resulting in postprandial hyperinsulinaemia and persistently elevated plasma levels of IGF-1, thus providing pivotal signals for mTORC1 activation (19). First evidence supporting a correlation between milk consumption and BMI has been provided by the Growing Up Today Study (10). Further support comes from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2004, which demonstrated that higher BMI percentiles among US White, Black, and Mexican-American children of age 2–4 years was associated with increased milk consumption (20). In accordance, Di Landro et al. (11) recently provided clinical evidence that acne risk increased with the frequency of milk consumption of adolescents. Remarkably, Arnberg et al. (21) reported that milk protein consumption (either daily intake of 35 g of whey, casein or skim milk protein) further increased BMI and C-peptide plasma levels in overweight Danish adolescents.

MILK CONSUMPTION AND INSULIN RESISTANCE

Elevated plasma concentrations of BCAAs leucine, isoleucine and valine, major constituents of milk proteins
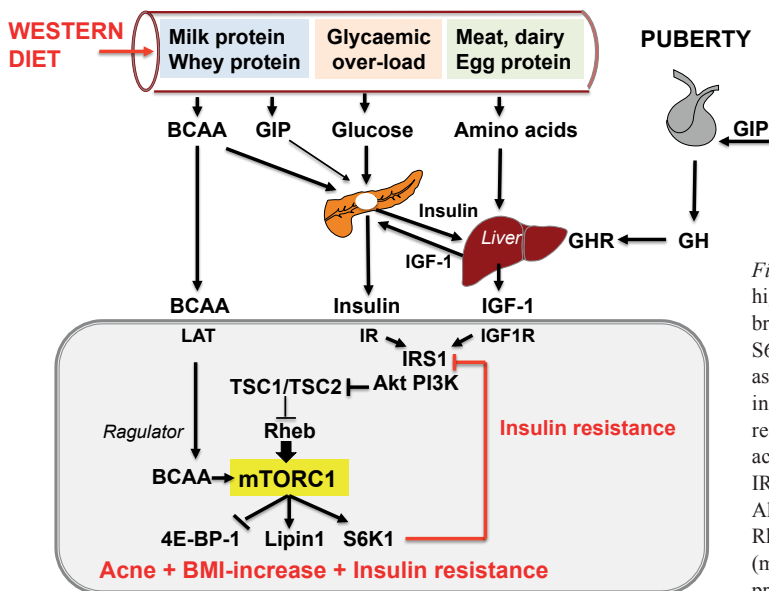

Fig. 2. Western diet composed of high glycaemic load and increased high milk/dairy protein consumption containing abundant amounts of branched-chain amino acids (BCAAs) both over-stimulate mTORC1-S6K1 signalling promoting exaggerated cell growth and proliferation as well as S6K1-mediated insulin resistance. GIP = glucose-dependent insulinotropic polypeptide; GH = growth hormone; GHR = GH receptor; IGF-1 = insulin-like growth factor-1, LAT = L-type amino acid transporter; IR = insulin receptor; IGF1R = IGF-1 receptor; IRS1 = insulin receptor substrate-1; PI3K = phosphoinositol-3 kinase; Akt = Akt kinase (protein kinase B); TSC = tuberous sclerosis complex; Rheb = ras-homologue enriched in brain; mTORC1 = mammalian (mechanistic) target of rapamycin complex 1; 4E-BP-1 = 4E-binding protein 1; S6K1 = S6 kinase 1.

and pivotal activators of the amino acid-sensitive enzyme mTORC1, have been associated with obesity and future insulin resistance in children and adolescents in the United States (22). There is accumulating evidence that high plasma levels of BCAAs are associated with insulin resistance (18). In fact, Hoppe et al. (23) have demonstrated that high intake of milk protein (53 g/day), but not meat (53 g/day) increased basal insulin serum levels and induced insulin resistance in 8-year-old Danish boys.

Thus, enhanced mTORC1 signalling results from high GL and milk consumption, which both play a fundamental role in the pathogenesis of food-aggravated acne. Exaggerated mTORC1 signalling induced by Western diet stimulates the important downstream target of mTORC1, the kinase S6K1, which negatively controls insulin signalling at the level of insulin receptor substrate-1 (IRS-1) phosphorylation (6, 19). Nutrient-mediated over-stimulation of mTORC1-S6K1-signalling thus induces insulin resistance, the characteristic feature of high milk consumption, acne and conditions associated with the metabolic syndrome (Fig. 2) (18–23).

INCREASED MILK CONSUMPTION, ACNE AND EARLY MENARCHE

The NHANES study also confirmed that increased milk consumption in children was related to an early onset of menarche (24). Remarkably, more severe comedonal acne has been associated with an earlier onset of menarche (25). Thus, increased milk and milk protein consumption is not only associated with acne (5–9, 11, 26–28) but also with early onset of menarche (24, 25). It is of most critical concern that early onset of menarche has recently been related to an increased risk of obesity, type 2 diabetes mellitus and metabolic syndrome in adult life (29–34). Thus, an appropriate endocrine, metabolic and growth balance during puberty and adolescence appears to be of critical importance for health in adulthood.

MILK CONSUMPTION DURING ADOLESCENCE AND RISK OF PROSTATE CANCER

A frequent history of more severe acne appears to be related to a higher prevalence of prostate cancer later in life (35, 36). The growth-promoting signalling system of milk may not only over-activate mTORC1-driven growth of sebaceous glands but may also affect mTORC1-mediated prostate morphogenesis and maturation during puberty (37). There is convincing evidence from molecular oncology that increased mTORC1 signalling steers cancer initiation and metastasis (38). It is thus of concern that epidemiological evidence from

Island emphasised an association between daily milk consumption during adolescence and increased risk for advanced prostate cancer later in life (39). Again, the time of puberty, which is associated with the highest incidence of acne, appears to be a most sensitive period affecting long-term prostatic tissue homeostasis (37).

"MILK GIANTS" VERSUS LARON DWARFS

Western diet, the maximised form of Neolithic nutrition, with highly over-activated mTORC1-signalling appears to promote a special human phenotype, the "milk giant" characterised by increased linear growth (40), increased BMI, obesity (10, 20, 21), frequent juvenile-onset myopia (increased vitreal chamber growth) (41), insulin resistance (23), type 2 diabetes and cancer (37, 42–44). This "maximised" growth phenotype exhibits a high prevalence of acne, a proposed indicator of exaggerated mTORC1-signalling. In contrast, humans like the Kitava islanders, who consume a Palaeolithic diet without grains and milk products apparently live on a normal insulin/IGF-1/mTORC1-axis, exhibit normal BMI, are insulin-sensitive, have very low prevalence rates of diseases of civilisation and do not exhibit acne, not even during their climax of puberty (3, 45–47). In comparison to the Kitava, untreated subjects with Laron dwarfism, who exhibit a genetic growth hormone receptor defect with congenital IGF-1 deficiency and thus abnormally decreased mTORC1 signalling are of short stature, but most importantly are protected against the epidemics of type 2 diabetes, cancer and acne (48–51). In patients with Laron syndrome the somatotropic axis is pathologically low. In humans consuming a Palaeolithic diet the somatotropic axis appears to in the normal range, whereas regular milk and dairy consumers exhibit an increased somatotropic axis with enhanced plasma levels of growth hormone and 20–30% increased IGF-1 levels compared to non-dairy consumers (52–57). IGF-1, the central growth hormone of puberty, is the most important stimulus for mTORC1-driven sebaceous gland growth and lipogenesis (58, 59). IGF-1 via mTORC1 activation up-regulates the activity of sterol response element binding protein-1 (SREBP-1), the key transcription factor of lipogenesis (60–62), as well as IGF-1/FoxO1-mediated up-regulation of androgen receptor signal transduction, which co-stimulates sebaceous lipogenesis (63–65).

Thus, the absence of acne in untreated Laron syndrome with low IGF-1/mTORC1 signalling, the absence of acne in Kitava islanders consuming Palaeolithic diet (no milk, no grains) with normal body shape and obviously normal mTORC1 activity, but epidemic acne in populations consuming Western diet, where milk/dairy intake and glycaemic load are abundant lead to over-activated mTORC1 signalling (Figs 2 and 3).
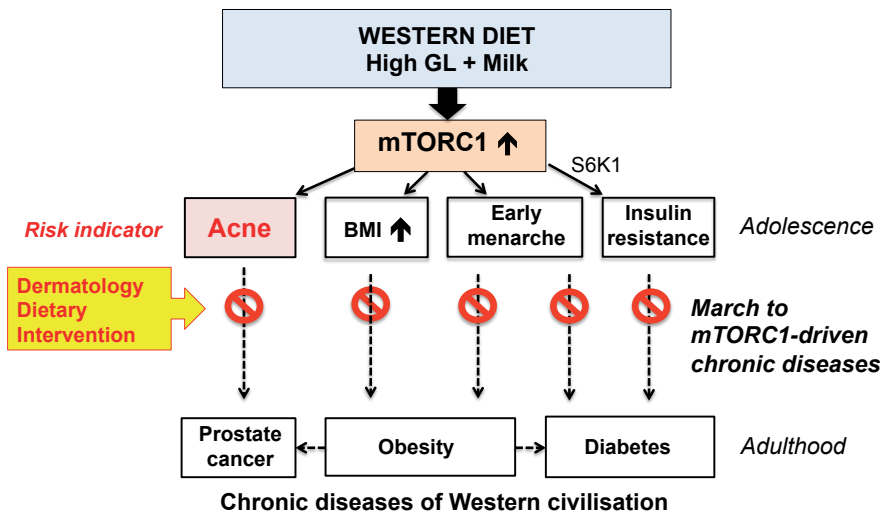
Fig. 3. Acne: a risk indicator of increased mTORC1 signalling on the march to chronic diseases of civilisation. Potential impact of dermatologic treatment for dietary prevention of acne and chronic diseases of civilisation by attenuating increased mTORC1 signalling.

CONCLUSION

Acne appears to be a visible indicator of systemically exaggerated mTORC1 signalling, an unfavourable metabolic deviation on the road to serious mTORC1-driven diseases of civilisation, especially overweight (increased BMI), obesity, arterial hypertension, insulin resistance, type 2 diabetes mellitus, cancer, and Alzheimer´s disease (42–44, 66–68). Increased milk consumption during adolescence may not only negatively affect sebaceous gland homeostasis but may exert long-term adverse health effects on other glands like the prostate. Epidemic acne is thus not a bagatelle but a constellation of exaggerated mTORC1 signalling, a metabolic deviation enhancing the risk for serious diseases of civilisation. During adolescence exaggerated mTORC1 signalling may not only affect sebaceous follicle homeostasis but may disturb normal sexual maturation and mTORC1-dependent morphogenesis (Fig. 3).

The role of high GL and milk consumption in the pathogenesis of acne has reached highest academic interest in the field of nutritional sciences and dermatology (69). Therefore, more clinical placebo-controlled randomised intervention studies with special attention to combinations of high GL and milk/dairy consumption are required. Dermatologists should not only focus on the treatment of acne's skin pathology, but should appreciate the underlying systemic effects of over-stimulated mTORC1 signalling induced by high GL and increased consumption of milk and milk products. The dermatologist, frequently involved in the treatment of adolescents during a vulnerable phase of metabolic programming, may not solely focus on treating acne's skin pathology but should appreciate the great chance for dietary intervention. Dietary attenuation of over-stimulated mTORC1 signalling may not only improve acne but may prevent the march to more serious chronic mTORC1-driven diseases of civilisation. In this regard, the most common acne vulgaris of adolescents of industrialised countries is not a "physiological" phenomenon of puberty, but represents a visible risk indicator already pointing to aberrant nutrient signalling promoting chronic epidemic diseases of civilisation.

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