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# Permanent impairment of insulin resistance from pregnancy to adulthood: The primary basic risk factor of chronic Western diseases

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## SUMMARY

Besides its well appreciated role in diabetes, obesity, and metabolic syndrome, insulin resistance (IR) is associated with smoking, use of hormonal contraceptives, androgens, glucocorticoids, beta-adrenergic blockers, thiazide diuretics, intake of food with high glycaemic index, and reduced physical activity. IR increases serum hormone levels of insulin and insulin-like growth factor-1 (IGF-1), which are most important mediators of cell proliferation, differentiation and inhibitors of apoptosis. Milk and dairy are introduced as new risk factors inducing IR, the physiologic growth-promoting principle of mammalian milk. This hypothesis explains IR as the underlying pathophysiologic mechanism of all major risk factors of chronic Western diseases. Evidence will be provided which supports that Western life style permanently boosts IR from intrauterine life to senescence. It becomes detrimental when the human intrinsic insulin/IGF-1-axis is continuously superimposed by external IR-potentiating effectors. This hypothesis can be proved by monitoring and proper adjustment of all aggravating effectors of IR. An all-encompassing consideration of IR-inducing risk factors from the beginning of life to adulthood appears to be of crucial importance for the prevention and treatment of chronic Western diseases.

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## Introduction

Common chronic diseases of Western societies, such as obesity, diabetes mellitus, metabolic syndrome, arterial hypertension, coronary heart disease, cancer, dementia, and allergic diseases are significantly influenced by dietary habits, smoking and inadequate physical exercise.

Insulin resistance (IR) is associated with metabolic syndrome, visceral adiposity and can progress to full type 2 diabetes mellitus [1]. Elevated serum levels of insulin and insulin-like growth factor-1 are associated with IR. Hyperinsulinaemia can worsen IR by down-regulation of the gen of insulin-sensitive glucose transporter-4 (GLUT-4) [2]. Insulin induces hepatic secretion of insu-

lin-like growth factor-1 (IGF-1) [3]. Growth hormone (GH) plays an important role in the induction of IR [4].

It is the intention of this hypothesis paper to provide evidence that IR and increased insulin/IGF-1 signalling is important for all life phases with physiologic growth requirements and is the major effector of all risk factors of chronic Western diseases. For a better understanding of the mitogenic and anti-apoptotic effects of insulin and IGF-1, their signal transduction pathways are briefly characterized.

### Insulin and insulin-like growth factor signalling

The insulin-like growth factor (IGF) system is essential for normal embryonic and postnatal growth, and plays an important role in the function of a healthy immune system, lymphopoiesis, myogenesis and bone growth among other physiological functions. Growth hormone (GH) and IGFs play an important role in growth and tissue homeostasis. GH secreted by the anterior pituitary binds to GH-receptor (GHR), expressed on most peripheral cells of the body. In peripheral tissues and predominantly in the liver, GH induces the synthesis and secretion of the 7.65 kDa polypeptide hormone IGF-1, the mediator of the growth-stimulating activity of GH. More than 90% of circulating IGFs are bound to IGF-binding protein-3 (IGFBP-3), the rest to IGFBP-1, -2, -4, -5, and -6, and less than 1% of IGFs circulate as free IGFs in the plasma. IGF-1 signal transduction is mediated primarily by the IGF-1-receptor (IGF1R), a

*Abbreviations:* ACTH, adrenocorticotropic hormone; AGA, appropriate for gestational age; AMP, adenosine monophosphate; AMPK, AMP-activated kinase; CVD, cardiovascular disease; DHEAS, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; GDM, gestational diabetes mellitus; GH, growth hormone; GHR, growth hormone receptor; GLUT, glucose transporter protein; IGF, insulin-like growth factor; IGFBP, IGF binding protein; IGF1R, IGF-1 receptor; IGF2R, IGF-2 receptor; IR, insulin resistance; LH, luteinizing hormone; LGA, large for gestational age; MAPK, mitogen activated protein kinase; PCOS, polycystic ovary syndrome; PGH, placental growth hormone; PI3K, phosphoinositide-3-kinase; SGA, small for gestational age; SREBP, sterol response element binding protein.

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tyrosine kinase receptor, which is able to form heterodimers with insulin receptor. IGF-2 binds to IGF-2-receptor (IGF2R), a scavenger receptor down-regulating IGF-2. IGF-2 is also able to bind to IGF1R. Insulin primarily binds to insulin receptor isoform-A and -B, but also binds with lower affinity to IGF1R. IGF-1 and IGF-2 bind to insulin receptor with lower affinity. IGF1R signal transduction is mediated primarily by the activation of the Ras-Raf-MAP kinase pathway and the phosphoinositide 3-kinase (PI3K)/Akt pathway. IGF-1 acts as a strong mitogen inducing cell growth and proliferation, but inhibits apoptosis [5]. The insulin receptor isoform-B is the form best known for the classic metabolic responses induced upon insulin binding and this isoform has low affinity for IGFs [5]. The insulin receptor isoform A arises from alternative splicing of exon 11 encoded by the insulin receptor gene. Activation of isoform-A by insulin or IGF-2 leads to mitogenic responses similar to those described for IGF1R. Increased signalling via insulin receptor isoform-A has been associated with the development of cancer [6]. In this regard, insulin and IGF-2 signal transduction via insulin receptor isoform-A and IGF-1 signalling via IGF1R amplify mitogenic responses [7–9].

### Physiologic insulin resistance in pregnancy

Hyperinsulinaemia and IR start to develop in the second half of pregnancy, when the maternal GH-axis shifts from pituitary-derived GH toward a predominance of placental GH (PGH) [10,11]. IR of normal pregnancy is a critical physiologic adaptation to limit maternal glucose uptake to ensure that an adequate supply of glucose is shunted to the growing fetus. The growing fetus requires 80% of his energy source as glucose. Normal pregnancy is characterized by an approximate 50% decrease in insulin-mediated glucose disposal in humans and a 200–250% increase in insulin secretion to maintain euglycaemia in the mothers [12,13]. Placental hormones, especially PGH, reprogram mother's physiology to become insulin-resistant. Both pituitary-derived GH and human PGH bind with the same affinity to GHR. Human PGH expressed in transgenic mice at levels comparable to those in the third trimester of human pregnancy, can cause severe total body IR as manifested by fasting and postprandial hyperinsulinaemia and increased serum IGF-1 levels [14]. PGH appears to mediate IR by increasing the expression of p85 regulatory unit of PI3K, resulting in marked reduction of insulin receptor substrate-1-associated PI3K-activity with subsequent reduction of insulin-sensitive GLUT-4 translocation to the plasma membrane [15]. The GLUT-1 present on both the microvillous and basal membranes of the syncytium, is the primary GLUT-protein involved in the transplacental movement of glucose. GLUT-3 is localized to the arterial component of the fetal vascular endothelium, where it may play a role in enhancing transplacental glucose transport [16].

A significant association between PGH and increase in IGF-1 and fetal growth has been demonstrated [11]. PGH is the major regulator mediating IR and maternal IGF-1 serum levels during pregnancy [11]. The GH-IGF-1 axis is closely related to feeding in the newborn [17]. In early pregnancy, maternal endocrine IGF-1 programs the placenta for increased functional capacity throughout gestation [18]. IGFs play a critical role in fetal and placental growth throughout gestation [19]. In the guinea pig administration of IGF-1 during early pregnancy increased placental transport of glucose and amino acids and increased placental and fetal weights [18]. Intriguingly, an early programming of the IGF-1-axis in the postnatal period has recently been demonstrated in humans [20]. Fetal growth depends on fetal levels of insulin and IGF-1 [21–23]. In newborn infants, IGF-1 and IGFBP-3 in cord blood showed significant correlations with birthweight and length [23].

### Physiologic insulin resistance in neonates, infants, and adolescents at puberty

GH levels are high in the fetus and newborn compared with those in later childhood and adults [24–31]. In postnatal life, nutrition, insulin, and IGF-1 largely regulate growth [17]. The ratio of IGF-1 to IGFBP-3 and the increase in IGFBP-2 suggest that the bioavailability of IGF-1 is increased in the fetus [32], and in early infancy [33]. IR and hyperinsulinaemia have been observed in prepubertal girls with premature adrenarche. In many of these girls, high IGF-1, low IGFBP-1, and higher DHEAS serum levels have been reported [34]. In healthy prepubertal girls as well as prepubertal girls with premature adrenarche, a positive correlation between IGF-1 and DHEAS serum levels has been observed [35]. Serum IGF-1 levels rise and fall in a pattern similar to serum DHEAS, and normal puberty is characterized by a state of transient IR associated with an increase in gonadal sex steroid production and adrenal androgens [34]. It becomes apparent that IR is associated with a physiologic shift of the somatotrophic hormone axis to support growth. The physiologic endpoint of this growth-promoting system is reached after puberty, when IGF-1 serum levels decline.

### Permanent insulin resistance: the key risk factor of chronic Western diseases

It will be shown that Western life style risk factors like obesity, consumption of cow milk and dairy products, hyperalimentation, increased intake of food with high glycaemic index, use of hormonal contraceptives, androgen abuse, common drugs like beta-adrenergic blockers and glucocorticoids, smoking, and inadequate physical exercise altogether permanently induce *pathologic IR* beginning already during pregnancy and fetal life persisting into adulthood. IR causes hyperinsulinaemia and elevated serum levels of IGF-1. Both hormones are potent mitogens, stimulate growth, cell proliferation, and exert anti-apoptotic activity, which have been correlated with the pathophysiology of metabolic disorders, cardiovascular diseases, cancer and neurodegenerative disorders [36–44].

### Underfeeding in the early postnatal period and reduced glucose tolerance later in life

Epidemiologic studies in humans have revealed links between perinatal food deprivation and adult incidence of obesity, type 2 diabetes, alterations of the hypothalamic–pituitary–adrenal axis, arterial hypertension and cardiovascular diseases [45–47]. An inverse relation between IGF-1 levels during the first months of life and IGF-1 levels in adulthood could be observed in 109 infants, which indicates that the IGF-1 axis may be programmed by diet early in life [20]. Low levels of IGF-1 in the postnatal period are associated with high IGF-1-levels in adolescence. Low levels of IGF-1 are reported in small-for-gestational age (SGA) newborn infants [17]. Low birthweight is a recognized risk factor for the development of type 2 diabetes and hypertension in adulthood [48,49]. Furthermore, longitudinal and cross-sectional studies have shown that low birthweight in girls with precocious pubarche are at risk for early onset of puberty and menses and further progress to anovulation, hyperinsulinaemic hyperandrogenism and polycystic ovary syndrome (PCOS) [50]. It appears that the IGF-1-axis in SGA-low birthweight newborns is drifted to higher IGF-1 levels in adulthood promoting the development of diabetes type 2, hypertension and PCOS. Low birthweight is associated with hypertension in adulthood. The compensatory drift of the IGF-1-axis to higher IGF-1 levels in individuals with low birthweight and low

IGF-1 levels to higher IGF-1 levels in adulthood may contribute to the development of hypertension. IGF1Rs are up-regulated by angiotensin II [51]. In hypertensive animals there is an increased IGF-1 mRNA and protein expression and IGF-1 plasma levels in hypertensive patients have been related to pressure load [52,53]. Based on these observations, the “thrifty hypothesis” has been established [48,54], from which the Predictive Adaptive Response (PAR) hypothesis was formulated [55–58]. Humans born with intrauterine growth retardation show catch-up growth during the first year of life [47,58,59]. Growth retardation followed by early catch-up growth exacerbates diseases later in life [60,61]. Preterm growth restricted babies displayed increased ghrelin and GH concentrations [62]. The fact that susceptibility to adult disease is affected by catch-up growth highlights the early postnatal period as a critical window. Underfeeding of mice during the early postnatal period (first two weeks of life) led to alterations in the somatotrophic axis which persisted throughout adulthood and caused hypertension and reduced glucose tolerance later in life due to insufficient insulin secretion [63].

### Overfeeding in the early perinatal period and insulin resistance later in life

Overfeeding of mice during the first two weeks of life resulted in alterations of the somatotrophic axis and induced IR and increased GH and IGF-1 in adulthood at the age of three months [63]. Postnatal overfed mice exhibited hyperinsulinaemia and persistent IR throughout adulthood. These animal experiments allow the conclusion that early perinatal under-nutrition or over-feeding modify the plasticity of growth through developmental changes of the GH–IGF-1-axis.

In industrialized countries, one of 10 newborns is affected with fetal macrosomia, which has been associated with an increased risk of developing obesity in childhood and diabetes type 2. The incidence of gestational diabetes mellitus (GDM) is increasing and occurs in 2.2–8.8% of pregnancies [64]. Risk factors of GDM are obesity, older age, family history, previous history of GDM, poor obstetric outcomes, ethnicity, PCOS, and hypertension [64]. Macrosomia is a common outcome of GDM. Among women with both normal and abnormal GDM screenings, increasing level of maternal glucose was linearly related to the risk of macrosomia. Women with excessive weight gain (more than 40 lb) had nearly double the risk of fetal macrosomia for each level of maternal glucose compared with those with gestational weight gain of 40 lb or fewer [65]. It can be concluded from these data, that the flux of glucose to the fetus is the critical factor for the development of fetal “over-feeding” leading to macrosomia. There are two important determinants which are responsible for fetal glucose supply, i.e., the size of the placenta and its glucose transport capacity, and the degree of IR of the mother which regulates maternal glucose supply. There is accumulating evidence that changes of the somatotrophic axis of the mother and her fetus are involved in the pathogenesis of fetal macrosomia.

Levels of IGF-1 and IGFBP-3 appear to be regulated by several factors, such as insulin, GH and maternal factors [23]. Levels of IGF-1 in cord sera of SGA-newborns (mean 48.7 ng/ml) were lower than those of newborns appropriate for gestational age (AGA) (56.4 ng/ml). Newborns large for gestational age (LGA) exhibited the highest IGF-1 cord sera levels (96.1 ng/ml) [23]. A recent study showed significantly higher insulin, leptin, IGFBP-3, and glucose concentrations in asymmetric LGA newborns than in symmetric LGA and AGA newborns [62]. Macrosomic neonates of diabetic mothers have significantly increased aortic intima-media thickness with higher serum IGF-1, IGFBP-3 and leptin concentrations than

those of controls [66]. Umbilical cord serum IGF-1 levels were correlated significantly with the IGF-1 concentrations of the mothers [67]. Umbilical cord serum levels of free IGF-1, total IGF-1, IGFBP-2 and leptin have been demonstrated as predictors of birthweight [68]. Recently, normal variations in maternal glycaemia on birth size and birth outcomes has been investigated in nondiabetic mothers [69]. Each 1 mmol/l rise in mother's 60-min glucose levels after oral glucose challenge in the 28th week of gestation resulted in a  $46 \pm 8$  g increase in offspring birthweight [69]. The mother's higher fasting glycaemia, lower insulin sensitivity, and lower insulin secretion were independently related to greater offspring adiposity at birth [69]. These observations in humans fit very well to postnatal over-fed mice, which developed persistent IR, increased body weight and hypertension compared with normal fed mice [63]. Thus, changes of the GH/IGF-1 endocrine axis during a critical perinatal window, during fetal and early postnatal life, determine somatotrophic function for the whole life. Experience with GH replacement therapy showed impaired insulin sensitivity even after two years of GH treatment, and increased fasting insulin levels after 10 years of GH treatment [70,71].

### Milk-induced insulin resistance

Milk is a complex, bioactive substance honed by evolution to promote growth and development of the infant mammal. Cow milk and dairy products are widely consumed by children and adults of Western societies well after the age of weaning. It is important to note that cow milk contains active IGF-1 (4–50 ng/ml) and IGF-2 (40–50 ng/ml) [72,73]. IGF-signalling belongs to the canonical pathways and networks regulated by estrogen and PGH in the bovine mammary gland. Cows treated with recombinant bovine GH to improve milk yield showed increased levels of IGF-1 in the milk [73]. High levels of IGF-1 are still detectable after pasteurization and homogenization of milk [74]. Intriguingly, bovine and human IGF-1 share the same amino acid sequences. Therefore, bovine IGF-1 can bind to the human IGF1R [75].

Several lines of evidence indicate that IGFs in milk can survive digestion and remain bioactive in the serum of milk consumers. Studies have demonstrated intact oral absorption and plasma bioactivity of IGF-1 in neonate and adult animals, especially when IGF-1 was administered together with the protease inhibitor casein, the primary protein in milk. High milk consumption in humans is associated with a 10–20% increase in circulating IGF-1 levels among adults and a 20–30% increase among children [36,37,76–81]. Girls with a milk intake below 55 ml/day had significantly lower IGF-1 serum levels compared to girls consuming more than 260 ml/day [82]. In 2109 European women, IGF-1 serum levels positively correlated with the intake of milk [83]. It is important to notice that dairy products increase IGF-1 levels more than any other dietary sources of protein like meat [36,37,78–83]. Moreover, milk-consumption elevated the ratio of IGF-1/IGFBP-3 indicating an increased bioavailability of IGF-1 [36,37,79].

Fermented and non-fermented milk products give rise to insulinaemic responses far exceeding what could be expected from their low glycaemic indexes (GI). Despite low GIs of 15–30, milk products produce three- to sixfold higher insulinaemic indexes (II) of 90–98 [84]. A large and similar dissociation of the GI and II exists for both whole milk (GI:  $42 \pm 5$ ; II:  $148 \pm 14$ ) and skim milk (GI:  $37 \pm 9$ ; II:  $140 \pm 13$ ) [85]. It has been suggested that some factor within the protein fraction of milk is responsible for milk's insulintropic effect [85]. Skim milk has been identified as a potent insulin secretagogue in type 2 diabetic patients [86]. Except for cheese with an insulin score of 45, milk and all dairy products

including yoghurt, ice cream, cottage cheese, and fermented milk products have potent insulinotropic properties [87].

The major protein fractions of cow milk is casein (80%), the remaining 20% are whey proteins. Both whey and casein contain specific proteins and peptides that may have growth stimulating effects. The effect of whey and casein fractions of milk on fasting concentrations of IGF-1 and insulin has been examined in 57 eight-year-old boys who received over seven days either casein or whey protein fractions with protein amounts of casein or whey similar to the content of 1.5 l skim milk. In the casein group, serum IGF-1 increased by 15%, whereas there was no change in fasting insulin. In the whey group, fasting insulin increased by 21%, with no change in IGF-1 [88,89]. The insulin response to a whey meal has been reported to be higher than that of a milk meal. This differential response suggests that the insulinotropic component of milk resides predominantly within the whey fraction of soluble milk proteins, whereas casein has a stronger IGF-1 stimulating effect than does whey [88,89].

Recently, the effects of whole milk or infant formula on IGF-1 serum levels and growth of infants from 9 to 12 months of age was investigated [90]. Intake of whole milk significantly increased IGF-1 in boys but not in girls. There was a significant correlation between weight and IGF-1 at 12 months and protein energy percentage was positively associated with IGF-1 consistent with the hypothesis that high milk intake stimulates growth [90].

#### Milk-induced increase of GH–IGF-1-axis

After a month of drinking 710 ml of ultra-heat treated whole milk daily, 10- to 11-year-old Mongolian children, previously not used to milk consumption, had a higher mean plasma level of IGF-1 and higher ratio of IGF-1/IGFBP-3 [91]. The mean serum GH and IGF-1 levels increased by 43.7% and 23.4%, respectively [91]. Thus, there is good evidence that milk consumption shifts the human intrinsic GH–IGF-1 axis to unusual high levels.

The milk-induced increase of GH, insulin and IGF-1 will interfere with the maternal intrinsic somatotrophic axis. Consumption of milk and dairy during early pregnancy may increase maternal serum IGF-1 levels, which could over-stimulate placental growth resulting in elevated placental glucose flux to the fetus [18]. Milk-induced hyperinsulinaemia may further increase the physiologic IR of pregnancy [92], thereby elevating the pool of maternal glucose for the fetus. Moreover, a large placenta may produce more PGH, the major regulator for fetal IGF-1 synthesis and fetal growth [11]. These considerations support the view that milk consumption during pregnancy may increase fetal growth and birthweight. Indeed, two recent studies show a positive correlation between consumption of milk during pregnancy and birthweight [93,94]. Pregnant women who consumed <250 ml milk/day gave birth to infants who weighed less than those who consumed more (3410 g versus 3530 g). Each additional cup of milk daily was associated with a 41 g increase in birthweight [93]. Most compelling evidence is provided by the Danish National Birth Cohort data on midpregnancy diet during 1996–2002, which included data from 50,117 mother–infant pairs. A linear correlation has been demonstrated between birthweight and quantified intakes of protein from dairy products, but not cheese protein or fat of dairy products [94]. Thus, biochemical and epidemiological data point to the important role of milk consumption during pregnancy for fetal growth and the development of fetal macrosomia. A milk-induced increase of maternal and fetal IR might change intrinsic hormonal growth axis in the mother and her fetus and induce epigenetic changes persisting throughout life.

#### Cow milk-based formula increases the newborn's insulin resistance

The insulinotropic effect of milk and dairy, which resides in the milk protein fraction, is an overlooked most important physiologic growth-promoting function of mammalian milk. The increase of GH, insulin, and IGF-1 by milk is comparable with the function of pituitary GH or PGH. Thus, after termination of intrauterine life, milk-mediated stimulation of the GH–insulin/IGF-1 signalling provides a mechanism for the maintenance of IR during the lactation period to support growth of the newborn. It has to be realized, that mammalian milk is a specific signalling system, which is adapted to specific growth requirements of the species. Milk is designed by evolution to induce partial IR to fulfil its physiologic growth promoting function. By superimposing the bovine milk–signalling system over the human newborn, the physiologic range of IR of the human newborns will be drifted to much higher ranges. This view is supported by the comparison of 43 breast-fed and 43 cow milk formula-fed one-week-old term infants. In comparison to breast feeding, higher postprandial insulin levels were measured in the cow milk formula-fed group [95]. Breast-fed infants at two months exhibited 28.1% lower IGF-1 serum levels in comparison with formula-fed infants [20]. Thus, humans use an inappropriate feeding system for their offspring. Cow milk consumption of the mother during pregnancy and infant feeding with cow milk-based formula may result in inadequate programming of the insulin/IGF-1 axis during fetal and postnatal life. Indeed, recent data point to an early programming of the IGF-1-axis within the first months of live [20]. This concept fits well to the observed increase in linear growth in milk consuming infants. Further evidence for the growth-promoting effect of milk comes from studies in developing countries. Milk and milk protein consumption is associated with an acceleration of linear growth and body height in industrialized countries [88].

#### Insulin resistance in infants and adolescents

In Western societies infants have daily access to milk and dairy products. In a one-week intervention study of 24 prepubertal eight-year-old Danish boys the effect of daily intake of 53 g of either lean meat or 1.5 l skim milk per day was studied with regard to insulin and IGF-1 responses. In the skim milk group, insulin and IGF-1 significantly increased by 105% and 19%, respectively [79]. However, there was no significant increase in either insulin or IGF-1 in the meat group. In the milk-group fasting insulin concentrations and relative IR increased significantly by 103 and 75%, respectively [79a]. After a month of drinking 710 ml of ultra-heat treated whole milk daily, 10- to 11-year-old Mongolian children, previously not used to milk consumption, had a higher mean plasma level of GH, IGF-1 and higher ratio of IGF-1/IGFBP-3 [91]. The mean serum GH and IGF-1 levels increased in these children after 4 weeks of milk consumption by 43.7% and 23.4%, respectively [91]. Thus, there is good evidence that milk consumption shifts the human intrinsic GH–insulin–IGF-1 axis to unusual high levels and induces IR, thereby fulfilling its evolutionary task, i.e., the promotion of growth.

It is of special concern that infants consume increased amounts of dairy in combination with carbohydrates with high glycaemic index like chocolate. The addition of an ordinary amount of 200 ml milk to a meal with a low glycaemic index increased the insulin response by 300% to a level typically seen from a meal with a very high glycaemic index like white bread [96]. Western lifestyle infant nutrition combining dairy with carbohydrates with high glycaemic index potentiates IR.

## Acne: a visible disease of exaggerated insulin resistance in puberty

Puberty, the final growth period, is mediated by partial IR. The increased secretion of pituitary GH increases hepatic secretion of IGF-1, the mediator of growth. From GH replacement therapies, it is known that GH increases IR [4]. Physiologic IR should be regarded as the driving force for the final growth spurt. Acne is the visible disease of increased insulin/IGF-1 signalling. Over-stimulation of sebaceous follicles by insulin and IGF-1 explains the epidemic of acne [97].

Acne is regarded as an androgen-dependent disease of the pilosebaceous follicle. Its course, however, corresponds less closely to plasma androgen levels than it does to GH and IGF-1 levels [98]. Significantly increased serum levels of IGF-1 have been observed in women with post-adolescent acne as well as adult acne patients [99,100]. In women, the total number of acne lesions correlated with serum IGF-1 levels. In Western societies, acne is a nearly universal disease afflicting 79–95% of the adolescent population. In men and women older than 25 years, 40–54% have some degree of facial acne, and clinical facial acne persists into middle age in 12% of women and 3% of men [101]. Epidemiologic observations point to the role of Western diet in the development or aggravation of acne. Cordain et al. [101] reported on 1200 Kitavan islanders of Papua New Guinea and 115 Aché hunter-gatherers of Paraguay who do not consume dairy products and have low glycaemic diets. No case of acne has been detected in these two non-westernized populations. Prospective cohort studies (Growing Up Today Study, based 1996) in 4273 teenage boys and 6094 teenage girls in the United States demonstrated a correlation between milk consumption and acne [102,103]. In the study of boys, the strongest association has been found between intake of skim milk and acne [103]. Sebaceous glands express IGF1R and IGF-1 has been recognized as a mitogen and morphogen of sebaceous glands [104]. GHR has been found on the acini of sebaceous glands [105,106]. Insulin as well as IGF-1 both stimulate sebocyte differentiation. However, when insulin or IGF-1 were administered together with GH, the effect on sebocyte differentiation was potentiated compared to either hormone administered alone [106]. These data are in good agreement with the clinical association between increased IGF-1 serum levels and increased facial sebum excretion in acne patients [107]. Both IGF-1 and insulin stimulate lipogenesis of sebaceous glands [106]. In sebaceous gland organ cultures, IGF-1 induced sebaceous lipogenesis [108]. In SEB-1 sebocytes, IGF-1 increased lipogenesis by induction of sterol response element-binding protein-1 (SREBP-1) [109]. SREBP-1 preferentially regulates genes of fatty acid synthesis. In the hamster ear sebaceous model, androgens rapidly induced the expression of SREBP-1 [110]. Insulin regulates SREBP-1c on the transcriptional level [111]. The importance of IGF-1 for lipid synthesis in SZ sebocytes and for keratinocyte proliferation has been demonstrated [112,113]. Acne in PCOS, which is associated with IR very well responds to the insulin-sensitizing agent metformin which increases insulin sensitivity and lowers increased insulin and IGF-1 serum levels [114]. Furthermore, metformin treatment prevented early puberty in girls with precocious pubarche [115]. Thus, it is conceivable that a rise in insulin and IGF-1 levels by milk consumption over-stimulates sebocyte proliferation and differentiation resulting in the development and progression of acne, a visible disease of exaggerated IR [97].

## Insulin resistance in adolescence and young adults

Besides the consumption of milk, dairy and high glycaemic food, adolescence is the period for the introduction of new risk factors, i.e., hormonal contraception, androgen abuse and smoking.

Oral contraceptives can cause deterioration in glucose tolerance and hyperinsulinaemia [116–118]. A significant deterioration of IR by etonogestrel (Implanon) has been observed in women with PCOS which is associated with IR [119]. A present study confirms that desogestrel, even when associated with low ethinylestradiol decreases insulin sensitivity, whereas ethinylestradiol in combination with chlormadinone acetate does not deteriorate insulin sensitivity [120].

“Industrialized” milk production by pregnant cows contributes to IR by increased amounts of estrogen, progesterone, and androgen precursors in the fatty fractions of milk, as these animals are kept permanently pregnant for up to 5 years to increase milk output [121–123]. Progesterone levels in fat of heifers and pregnant cows are found in ranges between 16.7 to 37.9 µg/kg and 239 to 336 µg/kg, respectively [124]. Thus, *milk fat-derived estrogen, progesterone, and androgen precursors* in fat of dairy products have synergistic effects with gestagen-containing hormonal contraceptives, thereby amplifying IR. Progesterone of pregnant cows accumulates in the animals' fatty tissues and its content in milk and milk products is dependent on fat content. Concentrations range from 1.4 µg/l in skim milk, 10 µg/l in whole milk, 41.8–72.7 µg/l in crème, and up to 300 µg/kg in butter [124]. A strong dairy consumer thus has a chance for an daily uptake of 40–50 µg of progesterone. This amount reaches ranges of oral gestagens prescribed for oral contraception. Progesterone induces IR and has been associated with breast development and tumorigenesis [125,126].

Another factor increasing IR becomes effective in boys and young men who start *abuse of androgens* to increase muscularity and physical appearance [127,128]. There is increasing evidence linking the excess of androgen and the development of IR. In women with PCOS, who are carriers of short CAG lengths of androgen receptor, an increase in testosterone impaired IR [129]. Shorter alleles of GGN and CAG repeat polymorphism in the exon-1 of the androgen receptor gene are, respectively associated with IR in men and with dyslipidemia in women [130]. Shorter androgen receptor CAG repeat length polymorphism has been correlated with androgenetic alopecia, hirsutism and acne [131]. Shortest CAG repeat length was found in men with androgenetic alopecia and acne ( $18 \pm 4$ ), and women with hirsutism ( $16 \pm 3$ ) compared to normal controls in men ( $22 \pm 4$ ) and women ( $21 \pm 3$ ) [131]. Early androgenetic alopecia has been identified as a marker of IR [132]. Recent studies have confirmed the association between androgenetic alopecia and IR in males [133,134]. Epidemiological studies have related androgenetic alopecia to severe young-age coronary artery disease, hypertension, diabetes mellitus, obesity and other IR-linked diseases [133,135–137]. Thus, androgenetic alopecia and persistent acne in adulthood should be regarded as important clinical markers of individuals with increased androgen receptor signal transduction associated with lower insulin sensitivity. These individuals will be most susceptible to exogenous androgens, and all other factors increasing IR. Of special public health concern is the fact that androgen abuse is combined with abuse of recombinant GH and insulin, further aggravating IR. In the bodybuilding and fitness centre environment, IR is further elevated by the intake of insulinotropic whey protein concentrates [128].

Smoking promotes IR, hyperinsulinaemia, dyslipidaemia with evidence of epithelial dysfunction as compared with non-smokers. Recent epidemiologic data have suggested that cardiovascular disease in smokers is primarily seen in those individuals who are insulin-resistant [138]. It is argued that IR is the major mechanistic link between cigarette smoking and cardiovascular disease. Acute smoking has been shown to increase ghrelin levels [139,140]. It has been recognized that ghrelin is a physiologic ligand of GH-secretagogue receptor and induces GH release from the pituitary [141]. Smoking of cigarettes with 2.0 mg nicotine content in comparison with those of 0.2 mg nicotine resulted in a higher GH plas-

ma level, which had not returned to baseline 60 min after smoking [142]. Higher insulin concentrations and IR predict the risk of exocrine pancreatic cancer in male smokers [143]. Insulin has growth promoting and mitogenic effects on pancreatic cancer cells [144]. Furthermore, hyperinsulinaemia, hyperglycaemia and/or IR have been identified as colorectal cancer risk factor in male smokers [145]. Insulin sensitivity varies in cigarette smokers, and there is evidence that cardiovascular disease (CVD) risk is greatest in those smokers who are insulin-resistant [138]. Intriguingly, it could be demonstrated that treatment of insulin-resistant smokers with the insulin sensitizing agent pioglitazone decreased CVD risk factors [146].

### Drug-induced insulin resistance

Unfortunately, many drugs used in the management of CVD or its associated risk conditions can affect glucose and lipid homeostasis and impair IR. Of special concern for long-term implications for increased risk of adverse outcomes are *thiazide diuretics*, *niacin*, and *beta-adrenergic blockers*, whereas *angiotensin-converting enzyme inhibitors* and *angiotensin receptor blockers* have beneficial metabolic effects on glucose homeostasis [147]. Like thiazide diuretics, beta-adrenergic blockers, especially non-selective and higher-dose selective agents, have been implicated in altering glucose homeostasis, primarily through inhibition of pancreatic insulin secretion and promoting IR [148–150].

*Glucocorticoids* display potent anti-inflammatory effects, and are therefore frequently prescribed to treat a wide variety of diseases. Chronic systemic exposure to glucocorticoids is associated with central adiposity, dyslipidaemia, skeletal muscle wasting, IR, glucose intolerance and overt diabetes. Recent progress in research into the role of glucocorticoids in the pathogenesis of IR and pancreatic beta-cell dysfunction has been made [151]. Glucocorticoid-induced protein catabolism has been linked to IR, and glucocorticoid-induced dyslipidaemia reduces insulin sensitivity [151].

### Metabolic syndrome, cardiovascular disease and insulin resistance

Impaired fasting glucose is a component of metabolic syndrome, which is a constellation of risk factors including abdominal

adiposity, hyperglycaemia, hypertension, and dyslipidaemia, all associated with IR. Hyperinsulinaemia and IR may be important in the pathogenesis of, and often coexist with obesity, hypertension, and diabetes [152,153] (Fig. 1). Obesity is recently regarded as a subclinical inflammatory condition that promotes the production of pro-inflammatory factors involved in the pathogenesis of IR [38]. Milk protein consumption and smoking, both inducers of IR, have been shown to be associated with increased risk for cardiovascular disease and mortality from coronary heart disease [138,154]. Over- and under-feeding of mice during the early post-natal period has been demonstrated to cause persistent metabolic consequences and changed the somatotrophic axis [63]. Overfed males displayed fasting hyperinsulinaemia and hyperglycaemic responses in the glucose tolerance test in adulthood [63]. Nutrient-restricted males also exhibited altered glucose tolerance due to insufficient insulin secretion [63]. Hypertension occurred in both under- and overfed adult mice [63]. Epidemiological studies in humans have revealed links between perinatal food deprivation and adult incidence of obesity, type 2 diabetes, alterations of the hypothalamic–pituitary–adrenal axis, arterial hypertension, and cardiovascular diseases [45,46].

### Cancer and insulin resistance

Metabolic syndrome, diabetes mellitus, and obesity are associated with increased cancer incidence. Hyperinsulinaemia and increased serum levels of IGF-1 have been associated with increased risk of cancer [7,9]. IGF-1 and insulin act through the tyrosine kinase growth factor signalling cascade enhancing tumour cell proliferation, but inhibit apoptosis [7,8]. Increased birthweight and height of the newborn are risk factors of breast cancer [155]. The intrauterine environment, i.e., pathologically increased insulin, IGF-1 and impaired IR, might contribute to the predisposition of women for breast cancer in adulthood [156,157]. Milk consumption, smoking, obesity, diabetes, and metabolic syndrome are all associated with IR and increased risk for the development of cancer.

### Allergic and autoimmune diseases and insulin resistance

The thymus is the only organ specialized in the establishment of immunological self-tolerance and stands at the crossroads be-

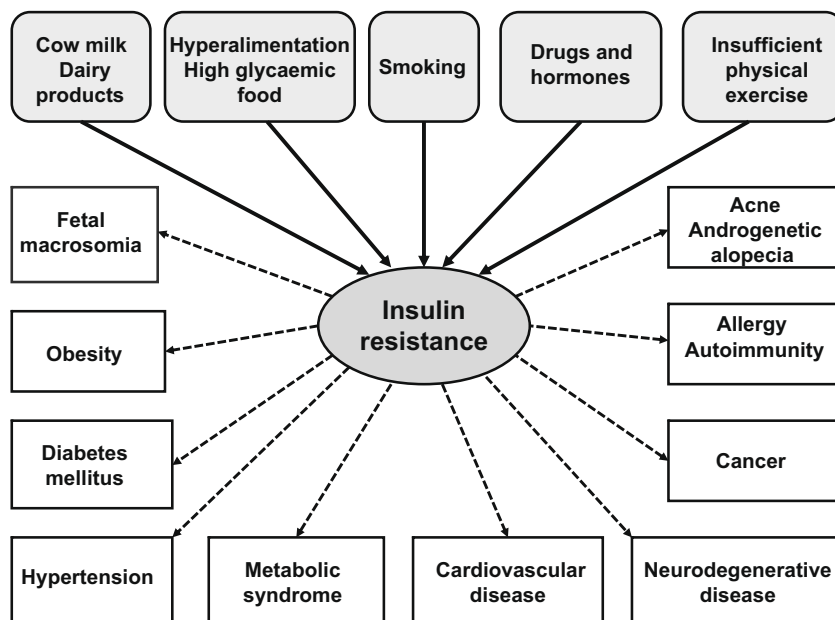


Fig. 1. Synopsis of risk factors resulting in impaired insulin resistance and associated diseases.

tween the immune and neuroendocrine systems [158]. The neuroendocrine system regulates the process of T-cell differentiation from the very early stages. T-lymphocytes undergo in the thymus a complex educative process that establishes central T-cell self tolerance of neuroendocrine principle. With regard to the insulin gene family, all members are expressed in the thymus network according to a precise hierarchy and topography of epithelial cells: IGF-2 (thymic cortex and thymic “nurse” cells) > IGF-1 (thymic macrophages) > insulin (medulla) [158]. The blockade of thymic IGF-mediated signalling at the level of IGF ligands or IGFs interferes with the early stages of T-cell differentiation in fetal thymic organ cultures [159]. Consumption of boiled farm milk during pregnancy was positively associated with increased immunoglobulin E (IgE) serum levels to cow milk and other food allergens [160]. The milk-induced maternal increase of the insulin–IGF-1 signalling might shift the insulin–IGF-1 axis in the fetal thymus, thereby damaging proper apoptosis of allergy- and autoimmune-prone T-cells explaining the co-appearance of atopic and autoimmune diseases later in life. Intriguingly, breast-fed humans have significantly lower serum insulin and IGF-1 levels than those fed on a cow milk-based formula [20,95]. An ever greater body of data point to the association between obesity and allergic diseases [161]. A high prevalence of atopic dermatitis is observed in Scandinavia, where cow milk consumption is very high. A lower prevalence of atopic dermatitis is reported in Mediterranean countries and Asia, where cow milk consumption is significantly less compared with Scandinavia [154,162]. Intriguingly, high cancer prevalence is found in Scandinavia, and low cancer prevalence in Mediterranean and Asian countries [123]. As the definition of atopic dermatitis had varying quality, and was imprecise in the majority of publications, the background cancer risk in patients with atopic dermatitis is hard to assess [163]. Of special concern will be long-term treatments with glucocorticoids which may have systemic effects and impair IR. Serum IgE score has been positively related with breast cancer in 103 women in comparison with 103 healthy controls [164]. A positive association of atopy assessed by allergen-specific IgE or skin prick testing has been observed with prostate cancer, but not with breast or colon cancer in a recent meta-analysis [165]. Smoking has been demonstrated to impair IR [139]. Studies in the last year have suggested that in utero exposures including tobacco smoke exposure may modulate both atopy and respiratory disease. There have been studies revealing *gene–environment interactions* between inflammatory pathway genes and in utero smoke exposure [166]. Thus, epidemiological and biochemical data underline the possible role of IR in the development of allergic diseases.

### Neurodegenerative diseases and insulin resistance

The major risk factor for the development of neurodegenerative disease is aging [167]. Mechanistic links between the aging process and toxic protein aggregation, a common hallmark of neurodegenerative diseases, has been revealed. Lifespan is regulated by at least three different mechanisms, one of which is the insulin/IGF-1 signalling pathway. The insulin–IGF-1 pathway is the major candidate to link aging, proteotoxicity and late-onset neurodegenerative disease [43,44]. It has been suggested that reducing insulin–IGF-1 signalling in the brain will enable cells to maintain the activity of protein quality-control mechanisms and clearance capabilities to a later age, thereby postponing the onset of neurodegenerative diseases [43]. Recent insights implicate the interconnection of IGF1R-signalling, regulation of lifespan, neurotrophin signalling and loss of neurogenic capacity and development of Alzheimer's disease [168]. Intriguingly, circulating IGF-1 is able to cross the blood–brain barrier and enter into the brain. Recent research points to the possibility that the brain is the site where reduced IGF-1 signal-

ling can consistently lead to an extended mammalian life span [44]. Recent evidence underlines the relationship between dementia and metabolic disorders such as diabetes, obesity, hypertension, and dyslipidaemia [169,170]. IR and hypersulinaemia are implicated in a number of pathophysiological processes related to Alzheimer's disease [171,172]. At the molecular level, IR and amyloid-beta ( $A\beta$ ) peptide disrupt common signal transduction cascades including the insulin receptor family/PI3 kinase/Akt/GSK3 pathway. Thus, both diabetes and Alzheimer's disease contribute to overlapping pathology, thereby compounding disease symptoms and progression [173]. Intravenous insulin infusion raised plasma  $A\beta_{42}$  levels in patients with Alzheimer's disease but not in normal adults, an effect that was exaggerated in patients with Alzheimer's disease with higher body mass index [171]. This finding illustrates the close relationship between IR and obesity, which may have particular implications for Alzheimer's disease and vascular dementia pathogenesis. Mechanisms regulating  $A\beta$ -clearance rather than production may be of special importance in late-onset Alzheimer's disease. Insulin may interfere with  $A\beta$ -degradation via its regulation of the metalloprotease insulin-degrading enzyme [174]. Thus recent evidence points to IR as a convergent mechanism that may underlie co-morbid metabolic disorders like diabetes, Alzheimer's disease and vascular dementia [170].

### Measures counteracting insulin resistance

It is of critical importance to avoid impaired IR in the perinatal period. Women who plan a pregnancy should optimize their body weight before conception. Consumption of milk and dairy products should be reduced during pregnancy. Weight control during pregnancy is of critical importance. Breast-feeding appears to be the only appropriate feeding type of human beings and will allow a normal programming of the somatotrophic axis. As long as the insulinotropic effect of cow milk is not antagonized, it has to be expected that cow milk formula feeding changes the GH–insulin/IGF-1-axis to higher levels resulting in impaired IR and IR-related disorders later in adult life [175]. Suppression of IGF-1 activity has recently been suggested for the treatment of endocrine disorders, atherosclerosis and cancer [42]. Insulin and IGF-1 lowering diets limiting milk intake and high glycaemic loads are promising approaches to improve acne [97,176–178]. There are further options to reduce IGF1R signalling by nutritional means. Polyphenols from soy and tomato products may counteract the ability of IGF-1 to stimulate proliferation and prevent apoptosis via inhibition of multiple intracellular signalling pathways involving tyrosine kinase activity [179]. Epigallocatechin-3-gallate, a major polyphenol found in green tea, regulates expression of IGF-1 and inhibits PI3 K/Akt and Ras/Raf/MAPK signalling pathways and directly inhibit IGF1R kinase activity [180,181]. Furthermore, it has been shown that green tea polyphenol extract regulates the expression of genes involved in glucose uptake and insulin signalling in rats fed a high fructose diet [182]. Green tea supplementation ameliorates IR and increases GLUT-4 content in a fructose-fed rat model [183].

Pharmacological down-regulation of IGF-1 by metformin or other insulin-sensitizing agents as well as selective inhibitors of IGF1R and its PI3K downstream signalling components might be promising new options for the treatment of conditions with high IGF-1-serum levels [42,184]. Novel IGF1R-targeting therapies have impressive antineoplastic activity in experimental systems [185]. Currently, there is increasing awareness of the role of platelet dysfunction, low-grade chronic inflammation, and thrombogenesis in the pathophysiology of IR, diabetes mellitus, and cardiovascular disease [186]. The positive influence of salicylates on IR are related to the activation of the NF $\kappa$ B pathway [186].

Physiologic insulin resistance		Abnormally impaired insulin resistance	
Fetal growth	IR ↑	IR ↑↑	Gestational diabetes, obesity ← cow milk and dairy intake
Postnatal growth Breast feeding	IR ↑	IR ↑↑	Cow milk based formula • <b>Abnormal programming of insulin-IGF-1-axis</b>
Prepubertal and pubertal growth	IR ↑	IR ↑↑	Cow milk, dairy, CH + high GI • <b>Acne, atopic diseases</b>
Adolescence		IR ↑↑	Smoking, hormonal contraceptives, androgens
Adult life		IR ↑↑	Diabetes mellitus, obesity smoking, insufficient exercise, steroids, β-blockers, thiazides • <b>Diabetes, CVD, cancer</b>
Menopause; Climacterium virile		IR ↑↑	Hormonal replacement and other adult risk factors • <b>Early onset of neuro- degenerative disease</b>
Senescence			

**Fig. 2.** Comparison between physiologic insulin resistance during normal growth phases (left panel) and abnormally impaired insulin resistance (right panel) during life in Western societies. CH = carbohydrate and CVD = cardiovascular disease.

Moderate-intensity aerobic exercise, such as brisk walking, decreases insulin, IGF-1 and IGFBP-3, and has been shown to improve survival in women diagnosed with breast cancer [187]. The AMP-activated protein kinase (AMPK) system acts as a sensor of cellular energy status and interacts with insulin, leptin and adiponectin. Activation of the AMPK underlies the glucose-lowering effects of metformin [188,189]. The AMPK system may be responsible for the health benefits of exercise [190,191]. It could be shown that metformin is an AMPK-dependent growth inhibitor for breast cancer and ovarian cancer cells [192,193].

## Discussion and hypothesis

This hypothesis shows for the first time that *all* chronic Western diseases may be related to a common underlying pathogenic key mechanism of well known risk factors of chronic Western diseases, i.e., insulin resistance. In order to assess an individual's personal risk constellation, all risk factors associated with IR have to be taken into account. These include the consumption of milk and dairy products, especially during the early programming of the insulin/IGF-1-axis in the perinatal period, the intake of food with high glycaemic index especially in combination with dairy products, the use of hormonal contraception, androgen abuse, prescribed drugs leading to further impairment of IR, as well as cigarette smoking.

All these nutritional, iatrogen and behavioural risk factors promote IR which should be regarded as the major cause of chronic Western diseases. It will be a challenge for most fields of medicine to recognize IR as the connecting mechanism of all serious life threatening risk factors from the beginning of life to senescence (Fig. 2). The awareness of the deleterious consequences of IR for human diseases and the identification of all related risk factors inducing or aggravating IR will be of great medical importance for the adjustment of a person's imbalanced insulin/IGF-1 "lifestyle"-axis and will have crucial impacts on the course of IR-related chronic diseases which overburden the health systems in Western societies.

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