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Review

Inflammatory markers in children and adolescents with type 2 diabetes mellitus

Thomas Reinehr

Department of Pediatric Endocrinology, Diabetes and Nutrition Medicine, Vestische Hospital for Children and Adolescents Datteln, University of Witten/Herdecke, Dr. F. Steiner Str. 5, D-45711 Datteln, Germany

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ABSTRACT

This review examines the potential relationship between serum inflammation markers and type 2 diabetes mellitus (T2DM). Inflammation markers have been proposed as prognostic markers for the development of T2DM and its complications. Furthermore, modulation of the inflammatory process may offer future treatment strategies for T2DM.

This review focuses on children and adolescents because there is usually little, if any, complications associated with other disease processes, use of medications, or active tobacco smoking. Furthermore, β-cell failure in young age cannot be solely explained by aging and exhaustion of β-cells due to insulin resistance.

Pediatric studies have demonstrated that pro-inflammatory cytokines TNF-α, IL-6, IL-1β, IFNγ, PEDF, and fetuin A were increased in insulin resistance, while the anti-inflammatory cytokines adiponectin and omentin were decreased. Furthermore, TNF-α, fetuin A, FGF-21 were altered in obese children with T2DM suggesting a direct involvement in β-cell failure. Future studies focusing on children and adolescents may facilitate our understanding of T2DM as an inflammatory disease process.

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most important health problems worldwide [1,2]. Socioeconomic factors such as increased obesity, physical inactivity and unhealthy diet have significantly increased the incidence of this disease over the last decade. T2DM is caused by insulin resistance impacting skeletal muscle, liver and adipose tissues and consequential islet β-cell exhaustion, followed by reduced β-cell function and loss of β-cell mass [3,4].

Over the last decade it has been proposed that T2DM might also result from chronic inflammation [5,6]. For example, highly sensitive C-reactive protein (hsCRP), a non-specific parameter of chronic inflammation, was increased in obese insulin resistant adults [7,8] and in obese adolescents with T2DM [9]. Inflammatory markers have been suggested as prognostic parameters for the development of T2DM and its complications [10]. For example, tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 were increased prior to T2DM onset in adults [11] or in gestational diabetes [12]. These inflammatory markers appear related to T2DM comorbidities that include nephro-, neuro- and retinopathy [10,13,14].

Modulating the inflammatory system has been proposed as therapeutic strategy for T2DM [10,13]: For example, salicylates, which are anti-inflammatory agents, have a hypoglycemic effect. Blocking the receptor of the pro-inflammatory cytokine TNF-α by etanercept decreases insulin resistance in obese rats. Additionally, the IL-1 receptor antagonist Anakinra promotes β cell secretory function. Antidiabetic medications do not only lower the blood glucose but also have anti-inflammatory effects. For example, glitazones reduce serum levels of CRP, TNF-α and other inflammatory markers.

The aim of this review is to summarize studies on serum inflammatory markers related to T2DM focusing on the pediatric population because studies in children have the advantage of not being influenced by other diseases, medications, or active tobacco smoking. Furthermore, β-cell failure in T2DM adults is a consequence of β-cell exhaustion resulting from long-term increased insulin excretion, ie, insulin resistance. However, β-cell failure in children likely results by β-cell exhaustion, genetic predisposition as well as other factors, ie, inflammatory cytokines. Therefore, studying children and adolescents with T2DM provides an ideal study model to evaluation the potential impact of inflammatory cytokines on β-cells.

2. Inflammation as trigger of insulin resistance and insulin secretion deficiency

Animal and in vitro studies implicate inflammation as an important pathway in T2DM pathogenesis and subsequent complications.

E-mail address: T.Reinehr@kinderklinik-datteln.de.

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Table 1
Inflammatory cytokines probably linked to type 2 diabetes mellitus.

Cytokine	Inflammatory effect	Origin
Adipocyte-specific fatty acid-binding protein (A-FABP)	Pro-inflammatory	Adipocytes, macrophages and endothelial cells
Adipolin	Anti-inflammatory	Adipocytes
Adiponectin	Anti-inflammatory	Adipocytes > cardiomyocytes, skeletal muscle
Adipsin	Activation of alternative complement system	Adipocytes
Fetuin A	Pro-inflammatory	Hepatocytes, tongue, placenta
Fibroblast growth factor (FGF)-21	Anti-inflammatory	Hepatocytes > adipose tissue, skeletal muscle, and pancreatic β-cells
Growth differentiation factor 15 = Makrophage inhibiting cytokine 1 (MIC-1)	Anti-inflammatory	Placenta > > Cardiocytes, adipocytes
Interferon gamma (IFNγ)	Pro-inflammatory	Ubiquitous
Interleukin-6 (IL-6)	Pro-inflammatory	Ubiquitous Fibroblasts, endothelial cells, and monocytes, macrophages in the visceral adipose tissue
Interleukin-8 (IL-8)	Pro-inflammatory	Ubiquitous
Leptin	Pro- and anti-inflammatory	Adipocytes
Lipocalin-2	Pro-inflammatory	Adipocytes
Monocyte chemoattractant protein-1 (MCP-1)	Pro-inflammatory	Ubiquitous
Omentin	Anti-inflammatory	Predominately in macrophages in visceral and epicardial adipose tissue
Pigment epithelium-derived factor (PEDF)	Pro-inflammatory	Human retinal pigment cells and adipocytes
Progranulin (PGRN)	Pro- and anti-inflammatory	Ubiquitous Abundantly in adipocytes and macrophages in adipose tissue
Resistin	Pro-inflammatory	Monocytes, macrophages, > preadipocytes
Tumor necrosis factor-alpha (TNF-α)	Pro-inflammatory	Ubiquitous Especially activated mononuclear phagocytes, antigen-stimulated t-cells, natural killer (nk) cells, and mast cells
Visfatin/PBEF/Nampt	Anti-inflammatory	Lymphocytes and adipocytes (especially visceral)

Importantly, cytokines influence tissue function in a para-, auto- and endocrine fashion and modulate the immune response. Cytokines may be pro- or anti-inflammatory (see Table 1).

2.1. Inflammation and insulin resistance

Pro-inflammatory cytokines promote insulin resistance via uncontrolled insulin receptor substrate production, whereas anti-inflammatory cytokines have the opposite effect [15–17] (see Fig. 1). Pro-inflammatory cytokines activate nuclear factor-κB (NFκB) and their downstream pathways [18]. In liver and adipose tissue, NFκB inactivates the insulin receptor (INSR) by decreased generation of insulin receptor substrates, thereby leading to insulin resistance [19]. This is achieved by serine phosphorylation of IRS [20]. In addition, inflammatory cytokines such as TNF-α upregulate the expression of suppressor of cytokine signaling (SOCS) proteins which bind to IRS to mediate its degradation [21].

Inflammatory cytokines related to glucose metabolism are produced in a variety of tissues such as adipose tissue (adipokines), liver (hepatokines), muscle and skeletal tissue. Adipocytes are the major cell involved in inflammation and insulin resistance in T2DM. Although it was shown that enlarged adipocytes produced pro-inflammatory cytokines, adipose tissue macrophages appear crucial for the production of adipose tissue-derived pro-inflammatory cytokines [22].

Macrophages can be classified into two distinct subtypes. The “classically activated macrophage” phenotype, ie, M1, secretes pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α [23]. The “alternatively activated macrophage” phenotype, ie, M2, produces anti-inflammatory cytokines such as IL-10. Obesity is characterized by a switch from the M2 to M1 phenotype [24].

Although macrophages are the most abundant leukocyte population in expanding adipose tissue, the adaptive immune system may also

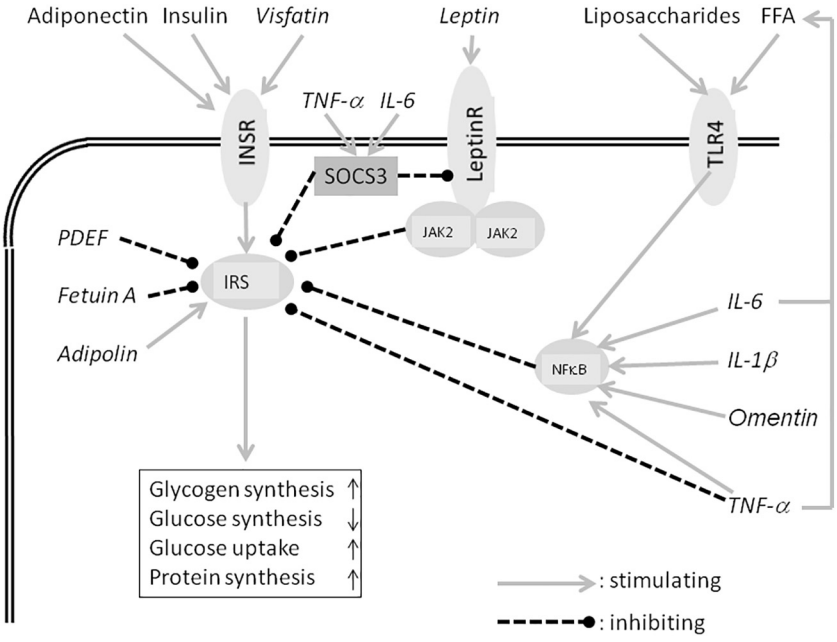

Fig. 1. Hypotheses based on animal and in vitro studies linking inflammatory cytokines to insulin resistance.
Cytokines in italics; abbreviations: FFA: free tatty acids, INSR: Insulin receptor, IRS: insulin receptor substrate, JAK2: Janus kinase, LeptinR: Leptin receptor, NFκB: nuclear factor κ B, SOCS3: suppressor of cytokine signaling 3, TLR: toll-like receptor.

contribute to obesity-induced inflammation [25]. Whether anti- or pro-inflammatory cytokines are produced depends on the regulation of a subset of T cells, ie, CD4-positive T helper (Th) cells, that can be further differentiated into Th1 and Th2 cells [26]. Th1 cells promote a pro-inflammatory cytokine profile whereas Th2 cells promote an anti-inflammatory response. Obesity modifies the balance of pro- and anti-inflammatory CD4+ cell subsets [22].

Of interest, visceral adipose tissue is characterized by macrophage infiltration and Th1 cells producing pro-inflammatory cytokines, whereas subcutaneous adipose tissue secretes larger quantities of anti-inflammatory and insulin-sensitizing cytokines [15,27–29]. Because visceral adipose tissue is regarded as a barrier between the gut and liver, the increased inflammation may by a consequence of microbiotic antigens which cross gut ("leaky gut hypothesis" [30]). Increased lipopolysaccharide absorption from the gut leads to decreased insulin secretion by activation of toll like receptor 4 and NF-kB (see Fig. 1).

The liver is populated with resident macrophages, ie, Kupffer cells, which produce inflammatory mediators that promote insulin resistance [22]. The muscle is another major site of insulin resistance in obesity and T2DM. Similar to adipose tissue, skeletal muscle macrophages exhibit a pro-inflammatory M1 phenotype accompanied with increased expression of inflammatory factors.

2.2. Inflammation and β-cell failure

Inflammatory cytokines cause insulin resistance, can lead to β-cell failure and subsequent development of T2DM [6,31–36]. Circulating inflammatory cytokines affect β-cell function by a variety of mechanisms. For example, inflammatory cytokines such as TNF-a, IL-1β and interferon-gamma (IFN-y) disrupt β-cell calcium regulation and subsequent insulin release [10]. TNF-α increases the expression of islet amyloid polypeptide in β-cells leading to accelerated death [37]. Islet amyloid polypeptide augments IL-1β production in islet cells [22,38]. The pro-inflammatory cytokine IL-1β appears to be a master regulator of islet inflammation in T2DM. IL-1β is a key contributor of β-cell failure through increased apoptosis [22,38].

Overall, there is a complex interplay between cells of innate and adaptive immunity and insulin resistance and β-cell function. However, these data from animal and in vitro studies have yet to be conclusively proven in humans.

3. Inflammatory markers produced ubiquitously

3.1. Tumor necrosis factor-alpha (TNF-α)

TNF-α is a pro-inflammatory cytokine synthesized as a 26 kDa transmembrane protein that undergoes cleavage by a metalloproteinase [16]. Activated mononuclear phagocytes antigen-stimulated T-cells, natural killer cells and mast cells are the major source of TNF-α. Although adipocytes are not the major source of TNF-α in obesity, macrophage infiltrates in visceral adipose tissue play a central role in the production of adipose-derived TNF-α [39]. TNF-α induces phosphorylation of IRS and thus attenuates the interaction of insulin with the insulin receptor [15] (see Fig. 1). Further, TNF-α enhances the activity of hormone sensitive lipase in adipose tissue increasing free fatty acid (FFA) release into circulation which also contributes to insulin resistance [40]. FFA cause insulin resistance via activation of toll like receptors and jun N-terminal kinase (JNK) [10]. Animal studies suggest that TNF-α is related to β-cell failure via amyloid peptide expression [6,31–36].

Studies in children confirmed these findings. TNF-α was associated with insulin resistance in children [9,41–45] according to studies in adults [8,46,47]. Furthermore, TNF-α was increased in obese adolescents with T2DM compared to BMI-, age-, and gender-matched adolescents without T2DM [9]. These findings foster the assumption that TNF-α is important in the genesis of insulin resistance and β-cell failure.

3.2. Interleukin-6 (IL-6)

IL-6 circulates in multiple glycosylated forms ranging from 22 to 27 kDa [15,27]. IL-6 is produced by many cell types including fibroblasts, endothelial cells, and monocytes-macrophages [13]. However, a significant proportion of the circulating IL-6 (15%–30%) is generated from adipose tissue macrophages. Interestingly, secretion of IL-6 is two to three times greater from macrophages in visceral vs subcutaneous adipose tissue.

IL-6 triggers the hepatic synthesis of CRP. IL-6 acts as a pro-inflammatory cytokine inhibiting the insulin signaling cascade by an impairment of insulin-induced insulin receptor and IRS activation [15] (see Fig. 1). The IL-6 receptor belongs to the cytokine class I receptor family that includes the JNK signal transduction pathway [13]. JNK activation by IL-6 induces STAT (signal transducers and activators of transcription) phosphorylation, dimerization, and translocation to the nucleus to regulate the transcription and function of an array of target genes including IRS, and NFκB in hepatocytes and adipocytes [13]. The interaction between IL-6 and the insulin pathway also involves mediating the interaction between SOCS proteins and the INSR [13]. Infusion of recombinant IL-6 in adults is answered by hyperglycemia and a higher hepatic glucose output [15]. Furthermore, IL-6 has a lipolytic effect followed by rising FFA levels in circulation [15].

Human studies confirmed experimental findings. IL-6 concentration was increased in obese insulin-resistant adults [7,48] as well as in obese insulin-resistant children [49,50]. There was no difference of IL-6 in children with and without T2DM [51]. These findings support the role of IL-6 in the genesis of insulin resistance but point against a direct involvement of IL-6 in β-cell failure.

3.3. Interleukin 1 beta (IL-1β)

The pro-inflammatory cytokine IL-1β not only worsens insulin resistance but also inhibits β-cell function while promoting apoptosis in mouse models [31,32,52]. IL-1β seems to be a key contributor of impaired insulin secretion by activation of NF-κB pathways and the generation of other inflammatory mediators, such as TNF-α and IL-1β itself, thus initiating a self-amplifying cytokine network [22,38]. The blockade of IL-1 improves hyperglycemia and β-cell function and reduces inflammation in animal models of T2DM [53].

Human studies confirmed these animal studies in part. IL-1β was increased in adults with T2DM [7,8,46]. A blockade of IL-1 improved hyperglycemia in adults with T2DM [31,54]. Obese children with insulin resistance demonstrated increased IL-1β vs lean counterparts [41,45]. In contrast, IL-1β concentration did not differ between obese adolescents with or without T2DM [9]. These findings do not support the hypothesis that IL-1β is involved in β-cell failure but confirm the role of IL-1β in the genesis of insulin resistance in children. However, serum IL-1β concentration may not reflect the local β-cell concentration and thus potentially explain animal model vs human study differences.

3.4. Interferon gamma (IFNγ)

IFNy is another pro-inflammatory cytokine presumably leading to β-cell dysfunction. It is secreted by Th1 cells [32]. IFNγ is an important immune-activating cytokine that can prime macrophages for activation and induce inflammatory responses [55].

Obese adults with T2DM demonstrated increased IFNγ [7,8,46,47]. However, obese adolescents with T2DM did not have increased IFNγ [9]. Obese children had increased IFNγ related to insulin resistance [56]. These findings do not support the hypothesis that IFNγ is involved in β-cell failure but confirm the role of IFNγ in the genesis of insulin resistance in children.

3.5. Progranulin (PGRN)

PGRN, a ubiquitous 593 amino acid glycoprotein, is abundantly expressed in adipocytes and macrophages [57–59]. It has both pro- and anti-inflammatory properties [57–60]. Full length PGRN has anti-inflammatory activity [61], while proteolytic cleavage of PGRN generates granulin peptides, some of which promote inflammation [62]. PGRN remarkably enhanced insulin resistance by binding to the TNF-α receptor inhibiting the insulin signaling cascade in cultured human adipocytes [58,63]. Furthermore, PGRN promotes insulin resistance by increasing levels of IL-6 [58].

Data in humans are conflicting. Some studies showed increased PGRN in obese adults with insulin resistance or T2DM, while others did not report any association [64–66]. Studies in obese children reported no difference in PGRN vs normal-weight counterparts as well as no relationship to parameters of insulin resistance [67,68]. Data in children with T2DM are lacking thus far. Therefore, PGRN does not seem to be related to insulin resistance in the pediatric population and the connection to β-cell failure is unclear.

3.6. Additional inflammatory cytokines

Several other generally expressed inflammatory cytokines have been suggested to be related to insulin resistance, but the underlying mechanisms have been poorly understood to date. For example, obese insulin resistant adults had increased monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8) [7,8,46,47]. Obese children with insulin resistance also demonstrated increased MCP-1 and IL-8 vs lean counterparts [41–45]. However, data concerning the concentration of these cytokines in adolescents with T2DM are not available. Therefore, it is unclear whether they play a significant role in insulin resistance or β-cell failure.

4. Adipokines

Cytokines secreted predominately from adipose tissue are called adipokines. Some of them also regulate inflammatory processes [69].

4.1. Leptin

Leptin, a widely known adipokine, is a 16 kDa peptide hormone mainly secreted by white adipose tissue [70]. It acts on the hypothalamus, leading to decreased appetite and increased energy expenditure, thereby regulating body weight [70]. Additionally, leptin acts on immune cells to stimulate the production of a spectrum anti- as well as pro-inflammatory cytokines [15]. Furthermore, binding of leptin to its receptor activates Janus kinase (JAK)2 which degenerates IRS (see Fig. 1) [71]. In contrast, leptin directly improved insulin resistance in mouse models of T2DM via increased FFA oxidation [73].

Because common obesity is as a leptin resistant state [74,75] this insulin sensitivity improvement of leptin may be diminished. An increased pro-inflammatory response is reported in leptin resistance during obesity [76]. Furthermore, TNF-α and IL-6 induce the activation of suppressors of cytokine signaling 3 (SOCS3), which is an anti-inflammatory cytokine that suppresses cellular responses to inflammatory cytokines and also exerts an inhibitory feedback loop to leptin and insulin signaling [72]. This overlap between both signaling pathways via SOCS3 is suggested as a concomitant development of insulin and leptin resistance in chronic inflammation, potentially contributing to insulin resistance due to leptin resistance [71,72].

The data in humans are conflicting. Some studies reported decreased leptin in adults with T2DM, while others showed increased or no differences in obese adults with and without T2DM [8,77–79]. In contrast to the hypothesis of leptin resistance as a trigger for insulin resistance, serum leptin was decreased in adolescents with T2DM vs adolescents without T2DM [80]. Studies in adults [46] or children [77] that reported increased leptin in T2DM have not adjusted controls to weight status, an important confounder because leptin has been strongly associated to fat mass. Therefore, it is not proven that leptin influences the development of insulin resistance or T2DM in adolescents.

4.2. Adiponectin

Adiponectin exists as a full-length protein of 30 kDa and as a number of multimeric complexes [15]. Adiponectin is produced by adipocytes but also by cardiomyocytes and human skeletal muscle [13]. Especially high molecular weight adiponectin is related to insulin sensitivity while failure in multimerarization of adiponectin is associated with insulin resistance [81,82]. Two isoforms of the adiponectin receptor have been identified: AdipoR1 and AdipoR2 [83]: AdipoR1 is expressed primarily in skeletal muscle, whereas AdipoR2 occurs mainly in the liver. Adiponectin acts as a hormone with insulin-sensitizing properties in vitro and in animal models and may also promote β-cell survival [84]. Even though adiponectin is secreted predominantly by adipose tissue adiponectin concentrations are negatively correlated with fat mass [82,85].

The reason for hypo-adiponectinemia in obesity and insulin resistance is unclear. IL-6 and TNF-α decreased adiponectin mRNA in vitro [86]. Therefore, hypo-adiponectinemia may be a consequence of chronic inflammation in obesity. Furthermore, prolonged exposure to insulin led to decreased adiponectin gene expression in adipocytes in vitro [86]. Therefore, hyper-insulinemia in insulin resistance might contribute to decreased adiponectin concentration.

Studies in humans were in line with the insulin-sensitizing effect of adiponectin. Adiponectin concentration was inversely correlated to insulin resistance in adults [82,87,88] and children [79,89]. Hypo-adiponectinemia correlated with the development of T2DM in adults [8,91,92], but the causal direction of this association is unclear. In manifest adult T2DM, some studies reported reduced adiponectin concentration, while others showed no change [8,44,46,79,93]. Decreased adiponectin was reported in children with T2DM [6,77]. After adjusting for weight status however, adiponectin did not differ in obese adolescents with and without T2DM, but did in obese children with and without insulin resistance [80]. These findings suggest that hypo-adiponectinemia was associated with insulin resistance but not T2DM.

4.3. Adipocyte-specific fatty acid-binding protein (A-FABP)

A-FABP belongs to the fatty acid-binding proteins and is present in adipocytes and macrophages [94]. Like most FABPs, A-FABP can bind with a variety of hydrophobic lipid ligands known to influence systemic inflammation [95]. Mice deficient in A-FABP are protected from development of hyper-insulinaemia, hyper-glycemia, and insulin resistance [94].

A-FABP concentrations were associated with insulin resistance in obese adults [94,96]. In contrast, there was no relationship between A-FABP concentrations and insulin resistance in obese children [97]. Data concerning A-FABP in adolescents with T2DM are not available so far. Therefore, there are no data in the pediatric population supporting the hypothesis that A-FABP is related to insulin resistance or T2DM.

4.4. Resistin

Resistin is a 12.5 kDa peptide produced by in monocytes and macrophages, and to a lesser extent by preadipocytes [15]. It was hypothesized that resistin has pro-inflammatory properties leading to insulin resistance [15]. Administration of resistin in healthy mice increased insulin resistance, whereas immunoneutralization of resistin in obese mice improved insulin sensitivity [98].

However, the role of resistin in human insulin resistance is less clear. Some studies documented that plasma resistin levels were

elevated in obese adults with insulin resistance [99], whereas others reported that high insulin-sensitive athletes had higher plasma resistin levels than obese subjects [100]. Data concerning resistin in adolescents with T2DM are not available so far. Resistin concentrations were not associated with insulin resistance in obese children [101]. This is in line with the current hypothesis suggesting that the main significance of resistin in humans is to regulate the inflammatory process rather than directly influencing insulin sensitivity [15].

4.5. Visfatin

Visfatin is a 52 kDa pre-B cell colony-enhancing factor expressed in peripheral blood lymphocytes [15] and visceral adipose tissue [102]. Its production is higher in visceral than in subcutaneous adipose tissue [102]. Similarly to insulin, visfatin in vitro enhances glucose uptake by adipocytes and myocytes, and inhibits hepatocyte glucose release [102]. Visfatin's insulin-like effects are activation of the IRS. Interestingly, visfatin and insulin have the same affinity for the insulin receptor but interact with the insulin receptor at a different site. Furthermore, visfatin regulates intracellular activity of the NAD/NADH dependent enzymes that are critical for glucose-stimulated insulin secretion in pancreatic β-cells [103].

Clinical studies in adults provided controversial findings concerning the role of visfatin in the glucose metabolism with positive, negative or no associations found [104–106]. In children no associations between visfatin and insulin resistance were reported [107]. Data concerning visfatin in adolescents with T2DM are not available so far. Therefore, there are no data in children supporting the hypothesis that visfatin is related to insulin resistance or T2DM.

4.6. Omentin

Omentin is a 38–40 kDa anti-inflammatory adipokine preferentially produced by macrophages in visceral and epicacardial adipose tissue [108]. However, expression of omentin in visceral adipose tissue is reduced in insulin resistance [108,109]. Omentin enhances insulin-stimulated glucose uptake in human adipocytes through Akt signaling of the GLU4 transporter in vitro [108,109]. Omentin leads to suppression of TNF-α induced activation of NF-κB cells [110]. Omentin upregulates adiponectin gene expression [111].

Data in humans confirmed animal and in vitro studies. In children, serum omentin levels correlated negatively with insulin resistance [112]. Obese children with insulin resistance had lower omentin serum levels compared to obese children without insulin resistance [113,114]. Data concerning omentin in adolescents with T2DM are not available so far.

4.7. Pigment epithelium-derived factor (PEDF)

PEDF is a 50 kDa secreted glycoprotein belonging to the serine protease inhibitor (serpin) family [15] and is secreted by the adipose tissue and human retinal pigment cells. Recombinant PEDF activates macrophages to release TNF-α and IL-1 [115]. Additionally, PEDF promotes lipolysis in an adipose triglyceride lipase-dependent manner and mobilizes FFA into systemic circulation leading to inflammation [15]. PEDF provokes kinase-mediated inhibitory Ser/Thr phosphorylation cascade of IRS that attenuates insulin signaling and induces insulin resistance in peripheral tissues [15]. Administration of recombinant PEDF reduces insulin sensitivity during hyper-insulinaemic-euglycaemic clamp in mice, whereas neutralization of PEDF restores insulin sensitivity [116]. PEDF expression in adipose tissue positively correlates with obesity and insulin resistance in mice [116]. Furthermore, PEDF might be the link between insulin resistance and acanthosis nigricans [117].

In adults, PEDF correlated better to insulin resistance than to the degree of obesity [118]. In children, plasma PEDF was positively associated with insulin resistance [119]. However, PEDF concentrations were similar in obese children with and without T2DM [120]. These findings support the role of PEDF in the genesis of insulin resistance, but do not confirm the hypothesis that PEDF is involved in β-cell failure.

4.8. Other adipokines

There are several other adipokines which have been proposed to link insulin resistance and T2DM via inflammatory processes (see Table 1). However, studies in adults are scarce and studies in children are lacking so far for these adipokines. One promising candidate is adipolin (CTRP12). It is a novel adipose-derived insulin-sensitizing adipokine [121]. Adipolin circulates in human and mouse plasma in two isoforms: full length fCTRP12 (40 kDa) and a cleaved gCTRP12 (25 kDa). In plasma, gCTRP12 (25 kDa) is the predominant isoform [122]. Enhancement of insulin signaling by adipolin was noted through increased activation of IRS [122]. Adipolin reduces macrophage infiltration in adipose tissue and may decrease pro-inflammatory cytokines. This suggests an anti-inflammatory role of adipolin in the insulin resistant state [121].

5. Hepatokines

Cytokines secreted by the liver, ie, hepatokines, have also been discussed relative to their role in chronic inflammation, insulin resistance and T2DM [123–131].

5.1. Fetuin A

Fetuin-A is predominantly produced in the liver and considered as a link between inflammation, insulin resistance, and T2DM [132]. The pro-inflammatory cytokine fetuin-A inhibited insulin receptor tyrosine kinase activity in muscle [133,134] and induced cytokine expression and low-grade inflammation in animal models [130]. Additionally, fetuin-A repressed adiponectin production in animals [130].

Increased fetuin-A was associated with degree of insulin resistance and presence of T2DM in adults [128,135]. Furthermore, fetuin A was linked to insulin resistance in obese children [9,136]. Serum fetuin-A was increased in obese adolescents with T2DM vs age-, gender- and BMI-matched adolescents without T2DM [137]. These findings indicate that fetuin-A is involved in the development of insulin resistance and β-cell failure in the pediatric population.

5.2. Fibroblast growth factor (FGF)-21

FGF-21 is another insulin-sensitizing hepatokine. It is mainly produced by the liver but also by other tissues including white adipose tissue, skeletal muscle, and pancreatic β-cells [138]. FGF-21 induces glucose uptake and decreases glucose concentrations in obese animals but the mechanism are poorly understood [125,139]. In obesity, a FGF-21 resistance state is hypothesized. FGF-21 resistance can be mediated through altered expression of both the FGF-21 receptor and the adapter molecule β-klotho [142]. Interestingly, TNF-α represses β-klotho expression and impairs FGF-21 action in adipose cells [131].

Adults with insulin resistance or T2DM had higher FGF-21 serum levels pointing to FGF-21 resistance [126,140,141]. In concordance, FGF-21 concentrations were higher in obese adolescents with T2DM compared to obese adolescents without T2DM [137]. These findings suggest a FGF-21 resistance state probably due to TNF-α in insulin resistance and β-cell failure in the pediatric population.

6. Impact of inflammatory cytokines in management of T2DM

In adults, inflammatory markers have been suggested as prognostic parameters for the development of T2DM and its complications

Table 2
Associations between inflammatory cytokines and T2DM in the pediatric population.

Insulin	Sensitivity	β-cell	Failure
Attenuating	Improving	Aggravating	Preventing
• PEDF • IL1β • IFNy • TNF-α • Fetuin A	• Omentin • Adiponectin	• TNF-α • Fetuin A	• FGF-21

including nephro-, neuro- and retinopathy [10–14]. Unfortunately, studies in children are generally lacking and likely attributed to rarity of T2DM in this age group. Today, inflammatory markers have no value for routine management of T2DM in children.

7. Conclusion

There are a growing number of inflammatory markers that could promote insulin resistance and β-cell failure ultimately resulting in the development of T2DM. Although this hypothesis could not be confirmed in the pediatric population, ie, no impact of PGRN, A-FABP, resistin, or visfatin on insulin resistance or T2DM, other inflammatory markers were significantly associated with insulin resistance and T2DM (see Table 2): Pro-inflammatory cytokines related to insulin resistance in children are TNF-α, IL-6, IL-1β, IFNγ, PEDF, and fetuin A. All were increased in the serum of obese children. Anti-inflammatory cytokines associated with insulin resistance in children are adiponectin, omentin, and FGF-21. Both adiponectrin and omentin were decreased in obese children. In contrast, FGF-21 was increased in insulin resistance hinting at a resistance state also for FGF-21. Pro-inflammatory cytokines, TNF-α and fetuin A, and the anti-inflammatory cytokine FGF-21 were altered in children with T2DM pointing towards a direct involvement in β-cell failure.

These pediatric data support the hypothesis that systemic inflammation is one link between obesity, insulin resistance and T2DM. Unfortunately, none have been proven of prognostic value vs traditional assessment, ie, measurement of hemoglobin A1c. Therefore, their value for routine clinical purposes remains to be elucidated. Understanding the complex pathways involving these inflammatory markers may facilitate the identification of potential therapeutic targets in treating insulin resistance and preventing T2DM.

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