Impact of Technologies on Diabetes-Related Comorbidities

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Type 1 diabetes (T1D) is one of the most common chronic diseases in childhood, with a progressively increasing incidence. T1D management requires lifelong insulin treatment and ongoing health care support. The main goal of treatment is to maintain blood glucose levels as close to the physiological range as possible, particularly to avoid blood glucose fluctuations, which have been linked to morbidity and mortality in patients with T1D.

type 1 diabetes | children | continuous glucose monitor | subcutaneous insulin infusion | automated insulin delivery | cardiovascular disease | nephropathy

1. Introduction

Diabetes care is focused on maintaining good metabolic control and reducing short- and long-term complications. The Diabetes Control and Complications Trial (DCCT) demonstrated that the lowering of hemoglobin A1c (HbA1c) levels by about 2% (9.0% to 7.1%) decreases the incidence of onset and progression of diabetic retinopathy, diabetic nephropathy and diabetic neuropathy by 47–54%, 39% and 60%, respectively, in both young adults (18–39 years old) [1] and adolescents (13–18 years old) [2] with a duration of diabetes of 1–15 years. The introduction of technologies and monitoring systems, which represent the standard of care for type 1 diabetes (T1D), have led to a reduction in the morbidity and mortality associated with the microvascular and macrovascular complications of T1D, although these events have not been fully eliminated. When comparing complication rates approximately 20 years earlier with those of the DCCT/EDIC cohort after 20 years of follow-up, the cumulative incidences of proliferative diabetic retinopathy (PDR) and nephropathy decreased from 50% and 35%, respectively, to 30% and 12%, respectively; rates of end-stage renal disease (ESRD) requiring dialysis or transplantation have also decreased. Rates of other clinically serious complications have also dropped dramatically.

2. Cardiovascular Disease and Type 1 Diabetes

Cardiovascular disease (CVD) represents a more common cause of death than microvascular complications in patients with diabetes. In particular, subjects diagnosed before 10 years of age presented a 30-fold increased risk of coronary heart disease and acute myocardial infarction in early adulthood than healthy peers [3].

In T1D, hyperglycemia influences CVD through multiple mechanisms. In detail, hyperglycemia enhances in cells the formation of diacylglycerol (DAG), a key activator of protein kinase C (PKC). Augmented PKC activation

determines the increased synthesis of matrix proteins (such as fibronectin and collagen), transforming growth factor (TGF)-β, that stimulate the thickening of the basement membrane; pro-inflammatory cytokines; vascular endothelial growth factor (VEGF), stimulating angiogenesis and vascular permeability; plasminogen activator inhibitor (PAI)-1, that prevents fibrinolysis; and reactive oxygen species (ROS) with consequent activation of oxidative stress that destroys arterial walls [4][5]. In addition, oxidative stress stimulates endothelial dysfunction by reducing the synthesis of NO, a crucial endothelial vasodilator [6].

Furthermore, hyperglycemia activates the polyol pathway, which converts excess intracellular glucose to sorbitol via the enzyme sorbitol dehydrogenase, finally resulting in the induction of intracellular oxidative stress with additional detrimental effects on arterial walls [7]. Moreover, chronic hyperglycemia activates non-enzymatic glycation of proteins, determining the formation of advanced glycation end-products (AGEs), interacting with the arterial wall through the related receptors (RAGEs) expressed on endothelial cells, thus exacerbating atherosclerosis. AGE/RAGE binding activates oxidative stress and NF-kB with the consequent trigger of inflammatory signaling, enhanced endothelium permeability, and endothelium dysfunction. NF-kB involvement determines by endothelial cells the expression of vascular cell adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1, and monocyte chemoattractant protein (MCP)-1, all contributing to increase the adhesion and attraction of monocytes and leucocytes [8][9][10]. Moreover, in endothelial cells, AGE/RAGE binding determines the production of endothelin-1, a strong vasoconstrictor [11]. AGEs also decrease the level of NO, a crucial endothelial vasodilator. AGEs trigger LDL oxidation as well as the formation of AGE-modified LDL (AGE-LDL) that, taken up by macrophages, leads to the secretion of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and TNF-α together with the of foam cell and atheromatous plaque formation. Interestingly, AGEs lead to thrombosis by enhancing the levels of tissue factor and decrease fibrinolysis by augmenting PAI-1 levels. Moreover, AGE/RAGE binding promotes smooth muscle cells proliferation and activation [12]. AGEs following the interaction with extracellular matrix proteins changes their turnover, with consequent extracellular matrix dysfunction and reduced flexibility of arteries [8][13]. In T1D patients, AGE pentosidine levels have been linked to coronary artery calcification [14]. Finally, in T1D patients, increased levels of methylglyoxal, the AGE main precursor, were linked to CVD in a 12-year follow-up study [15]. In addition, methylglyoxal has been linked to human carotid rupture-prone plaques [16]. It has also been demonstrated that hyperglycemia per se leads to endothelial dysfunction [17]. The main modifiable risk factor for decreasing CVD is represented by glycemic control. Current T1D treatment strategies and goals are based on the results of several studies of the DCCT and its epidemiological follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), which demonstrated that intensive insulin therapy aims to achieve glycemic control as close as possible to normoglycemia and is effective in delaying the onset and slowing the progression of microvascular and macrovascular complications observed in T1D [18]. There is evidence for a cardiovascular advantage of intensive glycemic control after long-term follow-up of cohorts affected with T1D. In the 9-year post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive arm had a significant 57% reduction in the risk of myocardial infarction, stroke, or cardiovascular death compared with those previously randomized to the standard arm [19]. The benefit of intensive glycemic control in this cohort persisted for several decades and was associated with a reduction in all-cause mortality. Chronic hyperglycemia can promote atherosclerosis, endothelial dysfunction, and arterial stiffness [20]. Furthermore, an association between glycemic

variability, CVD, and mortality, irrespective of mean glucose concentration, has been demonstrated [21]. T1D impairs endothelial function since childhood; in particular, the glucose variability can increase the vascular proliferation of smooth muscle cells, whereas hyperglycemia and the increase in fatty acid levels enhance oxidative stress and the production of advanced glycation end products [22][23]. In addition, hypoglycemia also contributes to cardiovascular complications. Hypoglycemia results in changes in hemodynamics, coagulation, arterial wall stiffness, cardiac electrophysiology, and autonomic function, explaining the observed associations between hypoglycemia and cardiovascular complications, including myocardial ischemia and cardiac arrhythmias [24]. Interestingly, subjects affected with T1D are more than twice as likely to experience cardiovascular mortality than the general population, even when they meet glycemic goals [25]. The progression of atherosclerosis begins in childhood, and young people with T1D can develop subclinical CVD even within the first 10 years of diabetes diagnosis [26]. CVD contributes to 25–50% of deaths in T1D subjects of less than 20-year diabetes duration, and this proportion increases with longer diabetes duration. DCCT/EDIC demonstrated that tighter glycemic control can improve cardiovascular risk factors, such as hypertension and carotid intima-media thickness, and even reduce cardiovascular events [1][3]. CGM devices and diabetes technologies, by improving glycemic trends and stability, may also have favorable impacts on T1D-associated complications. A large study from the Diabetes-Patienten-Verlaufsdokumentation (DPV) registry involving multiple diabetes centers in Germany, Austria, Switzerland, and Luxembourg found that the early initiation of insulin pump therapy within 6 months of diagnosis in people with childhood-onset T1D was associated with a better cardiovascular risk profile compared to those with delayed CSII initiation within 2–3 years of T1D diagnosis [27]. A reduction in the mean systolic blood pressure and an increase in high-density lipoprotein cholesterol (HDL-C), without significant relationships with diastolic blood pressure, low-density lipoprotein cholesterol (LDL-C), or triglycerides was observed [27]. Similar results were observed in a large T1D Swedish registry, which found that pump use was associated with a 45% reduction in coronary heart disease, 42% reduction in CVD, and a 27% reduction in all-cause mortality as compared to MDI use over a mean follow-up period of 6.8 years [28]. The decrease in cardiovascular mortality has been hypothesized to be related to a reduction in severe hypoglycemic episodes seen with insulin pump use. Less cardiovascular events, and lower mortality has been also associated with a longer duration of CSII use in T1D subjects [29]. A recent study compared indices of vascular function and myocardial performance in T1DM adolescents on MDI versus CSII. Infra-renal abdominal aorta (APAO), common carotid intima-media thickness (cIMT) and flow-mediated dilatation (FMD) represent the best non-invasive modalities to assess the vascular function and indirectly the myocardial status [30][31]. The mean cIMT and APAO values were higher in T1D patients than controls, and in those on MDI compared to those on CSII treatment [32]. Thus, the improving in glycemic control though CSII may reduce vascular alterations in T1D subjects.

3. Diabetic Nephropathy

Diabetic nephropathy (DN) indicates a specific kidney disease directly related to a long duration of diabetes and is often confirmed by histological lesions [33]. From 2002 to 2013, the prevalence of DN in children with T1D increased from 1.48 to 2.32 per 1000 [34], data only in part explained by a parallel increase in T1D prevalence [35]. Despite that, advanced DN is uncommon in pediatric patients, and the pediatrician's challenge is to quickly detect

early signs of renal involvement. The natural history of renal involvement in patients with T1D goes through several stages, from simple renal hypertrophy to several histological changes, which are the basis for an initial microalbuminuria (MA) followed by overt proteinuria that culminates in end-stage kidney disease [36]. The screening for detection of MA, as the earliest sign of DN, is recommended annually from puberty, at 10 years of age, and 5 years after T1D diagnosis [37]. Poor glycemic control, age at onset, duration of diabetes, puberty, high blood pressure, cigarette smoking, hyperlipidemia, genetic predisposition, and family history of diabetic complications are widely recognized as risk factors for developing DN [38]. In particular, puberty accelerates the development and progression of MA, conferring a three- to four-fold increase in the risk of MA after adjusting for other major risk factors [39].

DN development is primarily regulated by three pathways: (1) polyol and activation of PKC pathway. In detail, PKC pathway activation enhances the permeability of capillaries and triggers cellular stress and the expression of and transforming growth factor β1 (TGF-β1), exacerbating kidney injury [40]. Furthermore, polyol pathway activation alters the intracellular tension, enhances glycation as well as oxidative cell damage, and decreases anti-oxidation [41]. (2) Synthesis of AGEs in hyperglycemia breaks glomerular activity and leads to macrophage activation. In the kidney, AGEs/RAGE interaction determines chronic inflammation and oxidative stress, leading to kidney damage [42]. (3) Hyperglycemia leads to intraglomerular hypertension and glomerulus glomerular hyper filtration by triggering the local renin-angiotensin-aldosterone system. In the glomerulus, the elevated blood pressure increases renal vascular complications. Additionally, angiotensin II can lead to podocyte damage by augmenting ROS production [43]. Fibroblast Growth Factors (FGFs) also seem to have a key role, although further studies are needed. DN enhances the serum levels of the two most important members of this family of proteins, FGF21 and FGF23, which are positively related to renal damage. Consequently, FGF21 and FGF23 represent key biomarkers in order to predict renal disease progression, particularly in the early stage of DN [44].

Advances in technology for diabetes management have also led to improved pediatric nephrological outcomes via better glycemic control. The intensive treatment followed by the adolescent subgrouping in the DCCT study (in which the CSII) was associated with a reduction in the risk of developing MA by 10% compared to conventional treatment [2]. The protective effect of the intensive treatment on the development of nephropathy was maintained even during the 5–7 years of follow-up [45]. A higher TIR, a parameter associated with a lower risk of developing MA [46], can be easily obtained by the simultaneous use of real-time CGM and insulin pumps compared to intermittently scanned CGM and MDI [47]. However, whether CSII is preferable to MDI to ensure better glycemic control and decrease the risk of microvascular complications in the pediatric population is still a debated issue [48][49][50]. Schiel et al. showed that, in a cohort of 901 patients (age 11.5 ± 4.0), there were no differences between patients with CSII and MDI in respect of HbA1c, the mean amplitude of blood-glucose excursions, blood pressure, creatinine, and microalbuminuria [50]. These results were confirmed in a randomized control trial conducted by Blair et al. on 293 patients (median age of 9.8 years (range 0.7–16 years) that received CSII or MDI, without differences in terms of clinical benefits at 12 months of follow-up [49]. The artificial pancreas, a technology that minimizes user input by bridging continuous glucose monitoring and insulin pump treatment, is counted among the most innovative systems to manage diabetes. Karageorgiou et al. summarized in a meta-analysis the superiority of this system

compared to the standard sensor-augmented pump in the treatment of T1D pediatric patients, but further studies on the impact on microvascular complications are needed [51].

4. Diabetic Retinopathy

Diabetic eye diseases are a group of eye problems that affect people with T1D, and they include diabetic retinopathy (DR), diabetic macular edema, cataracts, and glaucoma. DR involves the growth of abnormal blood vessels in the retina and is considered the most severe entity that carries the risk of blindness in T1D patients. Pathological glucose metabolism has primary and secondary consequences on the retina [52]. Primary consequences are derived from the altered glucose and lipid metabolism that directly influences retinal cells such as neural cells, glia, microglia, Müller cells, and vascular cells, together with pericytes, endothelial cells, and intravascular cells. T1D secondary consequences on the retina arise from the primary insults. DR arises from different mechanisms; in detail, pro-inflammatory changes happen in the retina that involve NO, leukotrienes, cyclo-oxygenase [53], VEGF together with hyperglycemia itself [54] as well as the low activated state of circulating leukocytes. In detail, hyperinsulinemia and hyperglycemia can enhance CD40 levels in platelets and monocytes [55], whereas CD40 expression inhibition downregulated both leukostasis and ICAM-1 expression in endothelial cells [56][57]. High levels of CD40/CD40L, Toll-like receptors, ER stress, CCR5, and the CD11b+CCR5hi monocyte are implicated in the early onset of leukostasis [58] in T1D murine models. Consistently, in diabetes, the pro-inflammatory monocyte phenotype, with enhanced CD80 levels, has been reported [59]. The Epidemiology of Diabetes Interventions and Complications and The Diabetes Control and Complications Trial showed that optimal T1D management significantly reduces the risk of development of DR, as demonstrated by the reduction of DR prevalence from 14–20% before the year 2000 to 3.7–6% after 2000 [2][60][61]. Despite the pediatric population being the one with the lowest risk of DR, the related literature refers to a prevalence ranging from 2.3% to 44% [62][63]. Whereas the risk of developing DR is minimal in children under 10 years old, puberty is considered the most important risk factor for developing and progressing retinopathy [64][65]. The duration of T1D after menarche was related to a 30% excess risk of developing DR compared with T1D duration before menarche [64]. In childhood, the risk of developing DR is also related to diabetes duration [66][67] and glycemic control, as demonstrated by a large study from the United States that showed an increase of 20% (95% CI 6–35%) of the DR risk for every 1-point increase in HbA1c in children with T1D [68]. The technological evolution in diabetes screening and treatment has also impacted the natural history of DR in young people. The standard DR screening method, consisting of the dilated eye exam, is giving way to the digital fundus photography, obtained by non-mydriatic fundus cameras connected via telemedicine to teleretinal networks. This innovative screening method can safely and quickly be performed by non-specialist-trained operators without the need for pupil dilation. It has been shown to increase screening rates, reduce the distance traveled for screening, and be more sensitive than classical mydriatic ophthalmoscopy [69][70]. Furthermore, the Food and Drug Administration approved 2018 the first autonomous artificial intelligence system for DR screening [71], which has been shown to have 85.7% sensitivity and 79.3% specificity in pediatrics, but at this time, it is approved for use only in adults [72]. Recent advances in technology, through a better glycemic control, have also led to improvement in the DR pediatrics outcomes. Wysocka-Mincewicz et al. studied 175 children (mean age 12.74 ± 3.7SD) with optical coherence tomography angiography

and found a significantly lower fovea superficial vessel density, whole deep vessel density, parafovea deep vessel density and a larger foveal avascular (four early markers of DR) in the CSII vs. MDI group [73]. Additionally, Zabeen et al. found lower rates of retinopathy (OR 0.66, 95% CI 0.45–0.95, p = 0.029) in CSII group vs. MDI group of 989 patients (aged 12–20 years with a diabetes duration >5 years) [74]. Despite the verified role of continuous glucose monitor (CGM) in the improvement in glycemic control, few data are actually available on the effects of CGM use on development of DR in young people [75].

5. Diabetic Neuropathy

Diabetic peripheral neuropathy (DPN) is one of the main chronic microvascular complications of T1DM, which can lead to foot ulcers and lower-extremity amputations [76]. Generally, it occurs after at least 10 years of disease duration, and glycemic control represents the most important aspect of DPN management [77][78]. Clinical manifestations of DPN vary according to the type of nerve (large or small fibers) and organ involved (heart, bladder, intestine, etc.) [79]. DPN can develop as proximal asymmetric painful motor neuropathy, mononeuropathy, symmetric sensory-motor axonal neuropathy, and autonomic neuropathy [80]. However, symmetric sensory-motor axonal DPN shows the highest prevalence [80]. Axonal degeneration with demyelination has been reported in nerve biopsies [81][82].

In detail, damage to the Schwann cells and myelin sheath has been reported, with Schwann cells dissociating from axons both in unmyelinated and myelinated neurons [83]. Therefore, axonal impulse conduction and signaling are altered, and neurotrophic factors are reduced, leading to centripetal degeneration and distal axonal loss [84], with the longest nerve fibers at major risk of damage [83][85]. Different mechanisms have been proposed for DPN development, such as nerve barrier disruption and inflammation. The peripheral nerve microvessels are covered by a blood–nerve barrier (BNB). This barrier encloses the endothelial cells, pericytes, and basal lamina [86][87] and constitutes an important structure for transporting nutrients and protecting nerves [88]. The altered BNB function represents the first marker of damage associated with DNP development and progression. The increased permeability allows the transfer of high-molecular-weight proteins, such as immunoglobulin G and albumin, into the endoneurium [89][90]. The polyol pathway determining the hyperglycemia-induced flux alters membrane permeability and consequently molecule and electrolyte transport, perineurial basal or external laminae thickening, and thus edema. The last event determines subsequent ischemic nerve damage [91].

Cytokines, inflammatory cells, and growth factors are mediators of DNP development. In detail, hyperglycemia activates the cyclooxygenase-2 (COX-2) pathway in micro-vessels, leading to the development of oxidative and inflammatory stress in peripheral nerves [92]. A crucial role in DN development is determined by elevated AGE levels; consistently, AGEs are highly expressed in hyperglycemic status [93]. Additionally, an autoimmune etiology has been proposed for DNP but requires further investigation.

Emerging evidence suggests that glycaemic variability may be a crucial factor in the pathogenesis of DPN. The data from DCCT showed that intensive glucose monitoring decreased the incidence of DPN by 69% at five years [1]. A Cochrane systematic review and meta-analysis analyzed 17 randomized controlled trials (RCTs) examining

the role of glycemic control in the prevention of DPN (seven T1DM subjects, eight in people with type 2 diabetes (T2DM), and two in both). Improved glycemic control significantly reduced the risk of DPN in T1DM but not in T2DM subjects [94]. This difference could be due to heterogeneity in DPN assessments across trials. At present, the data about the impact of diabetes technology on the pathogenesis of DPN are few; furthermore, most of the studies performed are cross-sectional and use different systems for the assessment of DPN [95]. Longitudinal studies are needed to establish the role of CGM in the delay of the onset of DPN.

6. Impact of Type 1 Diabetes on Bone Health

T1D patients displayed a high risk of developing fractures with respect to the general population [96][97][98][99]. Newly diagnosed T1D can appear between the ages of 9 and 14 years [100], and childhood and adolescence represent crucial periods for optimal bone development [101], thus explaining the underlying abnormalities of bone health in these patients. In parallel, T1D is also associated with strong alterations in body composition, adiposity, and bone marrow adiposity [102][103][104][105]. Consistently, Abdalrahaman et al. reported that young women with childhood-onset T1D displayed a deficit in trabecular bone microarchitecture [106]. A detailed study has also been performed in T1D children and adolescents, with 10 out of 32 on CSII [31]. The authors showed that serum bone-specific alkaline phosphatase, C-terminal telopeptide of type I collagen (CTX), and total body (TB) and lumbar spine bone mineral density (BMD) SDS were lower compared with controls. Pediatric T1D patients also showed lower trabecular volume and trabecular numbers together with higher trabecular separation than controls. Although marrow adiposity was higher in patients than in the controls, even if not statistically significant, the marrow adiposity was inversely related to the trabecular number and directly to the trabecular space. Interestingly, they also demonstrated a positive correlation between the trabecular number and insulin dose, thus sustaining the role of insulin as an anabolic agent. In addition, the authors reported that bone formation was lower in children with poorer glycemic control but higher in children on CSII. Fractures appeared to a major extent in 31% of T1D children respect the 19% of controls. Moreover, the T1D children with a fracture history had poorer glycemic control and lower TB BMD with respect to T1D without fracture history [107]. Previously, researchers also demonstrated the key role of CSII with respect to MDI for both glycemic control and bone health [108][109]. In detail, researchers reported that glycemic control was better in CSII patients compared to MDI ones. Moreover, both glucose levels and HbA1c% were significantly decreased in CSII with respect to MDI patients. This improvement was also related to a major BMI-SDS and BMD in CSII with respect to MDI patients. The altered bone health in T1D is associated with the involvement of different biological effectors, such as Dickkopf-1 (DKK-1), sclerostin, and irisin.

6.1. Dickkopf-1 and Sclerostin

These represent two soluble inhibitors of the canonical Wnt signaling, a key pathway for bone-forming cell differentiation [110]. This signal involves the β-catenin translocation into the nucleus, where it can modulate the transcription of β-catenin dependent genes. In the absence of Wnt signal activation, β-catenin is degraded by the proteasome. This process allows to regulate the cytoplasmic concentration of β-catenin. To activate this signaling, the binding of the Wnt ligand to its Frizzled (FZD) receptor and Low-density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptors is necessary and determines the phosphorylation of LRP5/6 cytoplasmic tails and the

recruitment of β-catenin destruction complex to the plasma membrane. The protein reorganization allows the formation of the signalosome, a multiprotein complex. It blocks β-catenin degradation; thus, β-catenin accumulates into the cytosol and translocates into the nucleus binding TCF/LEF family of DNA-bound transcription factors to dismiss transcriptional repression and activate the transcription of β-catenin responsive genes, and thus osteoblastogenesis [110]. DKK-1 binds with high affinity to either of the two binding sites on LRP6 or LRP5, thus preventing Wnt ligand binding and the formation of FZD-LRP5/6 complexes [111][112][113]. An additional mechanism for DKK-mediated inhibition of Wnt signaling includes the endocytosis of LRP6, which is determined by DKK concurrently interaction with LRP6 and the transmembrane receptors Kringle containing transmembrane protein 1 (KREMEN1) or KREMEN2. This interaction activates the quick LRP6 removal from the plasma membrane [114][115][116], thus further sustaining DKK-mediated inhibition of Wnt signaling. DKK1 has a crucial role, particularly during the initial stages of osteoblast commitment and differentiation [89], and then its expression decays. Consistently, DKK1 overexpression decreases Wnt signaling and thus blocks osteoblastogenesis and increases adipogenesis because these two cells share a common precursor that, according to the microenvironmental stimuli, will differentiate accordingly. Consequently, in vivo, DKK1 overexpression is associated with reduced bone formation and osteopenia [117][118]. Differently, reduced DKK1 expression determines bone formation enhancement with consequent high bone mass in young growing mice [118][119]. Similarly, reduced DKK1 binding affinity to LRP5 in certain LRP5 gain of function mutations resulted in a high bone mass phenotype in these patients [120].

Sclerostin (the product of the *SOST* gene) is a secreted glycoprotein that inhibits Wnt signaling following the binding to the LRP5/6 extracellular domain [89] and thus directly competes with ligand binding. Loss of *SOST* leads to augmented canonical WNT signaling activation with consequently enhanced bone formation, which was more evident in female mice [121][122]. Patients and mice with *SOST* homozygous loss-of-function mutations [123][124][125] manifest sclerostosis, severely augmented bone mass and density [126]. Differently, transgenic mice overexpressing *SOST* show reduced bone mass [127][128][129]. It is also known that mechanical stimulation decreases osteocyte *SOST* expression, thus stimulating osteoblastogenesis, whereas mechanical unloading enhances *SOST* levels, thus inhibiting Wnt signaling together with osteoblast differentiation and activity [130][131][132].

Sclerostin is mainly expressed by osteocytes deeply embedded inside the mineralized bone matrix [133]. This exclusive “location” leads to the development of a sclerostin-neutralizing antibody (Romosozumab) approved for the therapeutic treatment of osteoporotic patients at high risk of fracture [134]. Different authors demonstrated the altered levels of DKK-1 and sclerostin in T1D [135][136][137][138][139][140], but they did not evaluate the differences arising from the use of different devices for insulin administration. Whereas previously, researchers deepened this issue. In detail, researchers demonstrated higher levels of DKK1 and sclerostin, inhibitors of bone formation, in T1D patients compared with the controls, but interestingly, consistently with a better BMD simultaneously, DKK1 and sclerostin levels reached the controls’ level in CSII patients, whereas with respect to the control and CSII groups DKK1 and sclerostin levels were elevated in MDI group, further supporting the crucial role of the type of therapy on bone health and glycemic control in T1D patients [108].

6.2. Irisin

Irisin originates from the Fibronectin type III domain, containing five proteins (FNDC5). This molecule in its structure has a signal peptide for ER [141], a hydrophobic transmembrane domain, a fibronectin III domain (that is the main part of irisin in the extracellular domain), and a carboxyterminal cytoplasmic domain. Following the N-glycosylation [142] in the ER and cleaving by disintegrin and metallopeptidase domain (ADAM) proteins (i.e., ADAM10) [143], irisin is secreted. This molecule is mainly secreted by skeletal muscle cells; initially, it was clarified its role in adipocyte trans-differentiation [144], and a few years later, its anabolic effect on bone (PNAS), leading to numerous related publications [145][146]. Myokine is involved in different bone diseases, including T1D [109], in which researchers explored irisin levels considering the different insulin devices. In detail, researchers reported the enhanced irisin levels in T1D patients compared to the controls, which correlated with both glycemic controls and bone status. In fact, irisin levels were negatively related to HbA1c%, years of diabetes, 25(OH)-Vitamin D, and positively with BMD and osteocalcin levels. Interestingly, in this case, researchers found the highest levels of irisin in CSII patients compared to MDI and control groups.

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