Acta Diabetol (2015) 52:433–443
DOI 10.1007/s00592-014-0635-6

REVIEW ARTICLE

Insulin and GH–IGF-I axis: endocrine pacer or endocrine disruptor?

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Received: 1 April 2014 / Accepted: 23 July 2014 / Published online: 14 August 2014

Abstract Growth hormone/insulin-like growth factor (IGF) axis may play a role in maintaining glucose homeostasis in synergism with insulin. IGF-1 can directly stimulate glucose transport into the muscle through either IGF-1 or insulin/IGF-1 hybrid receptors. In severely decompensated diabetes including diabetic ketoacidosis, plasma levels of IGF-1 are low and insulin delivery into the portal system is required to normalize IGF-1 synthesis and bioavailability. Normalization of serum IGF-1 correlated with the improvement of glucose homeostasis during insulin therapy providing evidence for the use of IGF-1 as biomarker of metabolic control in diabetes. Taking apart the inherent mitogenic discussion, diabetes treatment using insulins with high affinity for the IGF-1 receptor may act as an endocrine pacer exerting a cardioprotective effect by restoring the right level of IGF-1 in bloodstream and target tissues, whereas insulins with low affinity for the IGF-1 receptor may lack this positive effect. An excessive and indirect stimulation of IGF-1 receptor due to sustained and chronic hyperinsulinemia over the therapeutic level required to overtake acute/chronic insulin resistance may act as endocrine disruptor as it may possibly increase the cardiovascular risk in the short and medium term and mitogenic/proliferative action in the long term. In conclusion, normal IGF-1 may be hypothesized to be a good marker of appropriate insulin treatment of the subject with diabetes and may integrate and make more robust the message coming from HbA1c in terms of prediction of cardiovascular risk.

Keywords IGF-1 · Diabetes · Insulin · Cardiovascular risk · Growth hormone

Managed by Massimo Federici.

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Introduction

Diabetes mellitus is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications [1]. Although therapeutic strategies of diabetes mellitus are manifold and attention to the problem is growing in the scientific community, the incidence of the disease is alarmingly increasing. In fact, approximately 360 million people had diabetes in 2011, of whom more than 95 % with type 2 diabetes. This number is estimated to increase to 552 million by 2030, and it is thought that about half of those will be unaware of their diagnosis [2, 3]. It is also estimated that about 300 million of people may have alteration of glucose metabolism such as impaired fasting glucose, glucose intolerance, both often referred as "prediabetes," gestational diabetes and euglycemic insulin resistance [4, 5]. A total of 281 million men and 317 million women worldwide died with diabetes mellitus in 2011, most from cardiovascular diseases related to diabetes. The healthcare expenditure for diabetes in Europe was about 75 billion euros in 2011 and is projected to increase to 90 billions by 2030 [3]. In the USA, the estimated national cost of diabetes in 2012 was 245 billion dollars, of which 176 billions (72 %) representing direct healthcare expenditures

attributed to diabetes [6]. Based on these epidemiological data, a first challenge is to prevent diabetes in the general population by implementing beneficial lifestyle interventions [7]. In patients with diabetes, however, the challenge for clinicians is to choose the best therapeutic approach which should be at the same time effective and safe (e.g., the possible association recently hypothesized of insulin exposure and cancer risk). As a matter of fact, type 2 diabetes is not just dysglycemia but a complex interplay of pathophysiological mechanisms which operate involving multiple organs. Management of this complexity is difficult because such interplay differs in each patient and reliable clinical and biochemical markers of individual diabetic phenotypes are still largely lacking [8, 9]. Moreover, there is also a need for new and precocious biomarkers able to identify early patients at risk to develop chronic and irreversible complications of diabetes.

Over the recent years, several studies have investigated the interplay existing between growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis and diabetes mellitus and its treatment. GH and IGF-I secretions are influenced by metabolic signals [10] and derangements of GH/IGF-1 axis may occur in patients with diabetes mellitus potentially influencing the response to anti-diabetic treatments and the outcome of disease [11, 12].

This review will deal with the physiology of insulin and GH/IGF-1 actions, the pathophysiological and clinical aspects correlated with the derangement of GH/IGF-1 axis in patients with diabetes mellitus with focus on the interplay between insulin and IGF-1 in modulating glucose metabolism and influencing cardiovascular and neoplastic risk of patients with diabetes.

Insulin central and peripheral actions: physiology and pathophysiology

Insulin is generally treated as a peripheral hormone controlling glucose metabolism and glucose transport in the liver and muscles. In reality, although glucose metabolism in the brain is largely non-insulin dependent, insulin may exert a relevant activity also in the central nervous system, where insulin receptors (IRs) are located. In fact, insulin crosses the blood–brain barrier with a carrier-mediated process by a specific transport system coupled to IRs in cerebral microvessels [13–17]. IR is a member of protein kinase receptor family that is composed of two α-subunits and two β-subunits which are linked by disulfide bonds. Binding of insulin to α-subunits eventually leads to the activation of tyrosine kinase activity and initiation of insulin actions [18]. Also the IGF-1 receptor (IGF-1R) is a tetrameric glycoprotein that belongs to the receptor tyrosine (Tyr) kinase superfamily. It is composed of two α (120–135 kDa) and two β (95 kDa) subunits [19–22]. Due to structural and functional homology, insulin and IGF-1 can bind to (and activate) both IR and IGF-1R [23].

Insulin can also be synthesized in specific areas of the brain in small quantities [24, 25]. Studies suggest that cerebral glucose metabolism may be controlled in part directly or indirectly by neuronal insulin/IR signaling pathways [26–30]. Insulin signaling in the brain limits food intake. In fact, insulin secretion over the long term may function as a negative feedback signal of recent energy intake and body adiposity [31]. Under supra-physiological glucose levels, brain insulin signaling activation could result in hyperpolarization of glucose-sensing neurons decreasing body weight [20, 32, 33]. Conversely, impairment of brain insulin signaling (as it occurs in peripheral insulin resistance) might promote a feedback inhibition of IR. This leads to increased body weight by the activation of arcuate neurons containing NPY, AgRP and GABA [20, 31, 32, 34]. Interestingly, long-term central insulin signaling on body weight in humans has been suggested to have sex-dependent results. In fact, it may cause weight loss in men and inducing increase in water storage and weight gain in women [35]. Insulin was also hypothesized to play a role in protecting the neurons from oxidative stress and apoptotic death [36, 37]. In type 2 diabetes, insulin resistance is accompanied by down-regulation of insulin transport into the brain. Consequently, decreased cerebral blood flow, impairment of oxidative glucose metabolism and possibly progressive impairment in learning, memory and cognition may occur [32, 38–42]. The effects exerted by insulin at the peripheral level are better known with respect to the central ones. Insulin binding to the IR regulates the uptake of glucose from the circulation by inducing the translocation of glucose transporters from the cytoplasm toward the plasma membrane [39, 40, 43]. Insulin promotes glucose uptake in fat and muscle tissue, stimulates glycogen synthesis in liver and muscle and hepatic and adipocyte lipogenesis, and inhibits hepatic glucose production and adipocyte lipolysis. Finally, insulin is also a growth factor which determines cell growth and inhibits cellular apoptosis via the Ras–Raf–mitogen-activated protein kinase signaling pathway [44–46]. The mechanism of insulin resistance involves only the metabolic pathway of insulin signaling and not the mitogenic pathway [47]. Several studies demonstrated that inappropriate fat accumulation in muscle cells or the release of inflammatory cytokines by fat cells may affect the GLUT-4 pathway [48–51]. When the adipose tissue cannot fulfill its normal storage and lipo-regulatory function, insulin action could be compromised and insulin resistance may develop [48, 52–55].

GH/IGF-1 axis and insulin in physiology

Growth hormone is produced and secreted by somatotropes in the anterior pituitary in a pulsatile manner, mainly under hypothalamic control. The hypothalamic factors involved in GH regulation include GH-releasing hormone and somatostatin, which stimulate and inhibit secretion, respectively [10]. In addition to classic and non-classic hypothalamic peptides, many other neuropeptides (such as galanin), neurotransmitters (e.g., acetylcholine), metabolic signals (such as hypoglycemia, amino acids and free fatty acids) and peripheral hormones (e.g., IGF-1, thyroid and sex hormones and glucocorticoids) are involved in the modulation of GH secretion [56–61]. GH acts by inducing the synthesis of IGF-1 in the liver [10]. IGF-1 is a peptide hormone that shares nearly 50 % amino acid sequence homology with proinsulin, and, like insulin, is composed of an alpha and a beta chain connected by disulfide bonds [62]. Besides GH, the liver synthesis of IGF-1 is regulated by insulin. Studies in vitro demonstrated that insulin stimulates IGF-1 synthesis by hepatocytes in the absence of GH and the effects of insulin are additive to those of GH by increasing liver GH receptors and acting at post-receptor level [63].

The physiology of IGF-1 is complex because it acts as a circulating hormone and as a local growth factor [64]. In contrast to insulin, which is largely unbound to any transport molecules, as much as 99 % of IGF-I in circulation is bound to one of the six IGF-binding proteins (IGFBPs), mainly IGFBP-3 and IGFBP-5 [65]. Under normal circumstances, IGFBP-3 and IGFBP-5 are saturated. Therefore, abrupt changes in IGFBP-1 and IGFBP-2 that are not saturated and that occur as a result of changes in either nutrient intake or insulin secretion can result in major changes in free IGF-I and thereby regulate tissue responsiveness [66]. Indeed, insulin down regulates the synthesis of IGFBP-1, IGFBP-2, and, although to a lesser extent, IGFBP-3 from the liver leading to an increase in free IGF-1. From this point of view, insulin increases both synthesis and bioavailability of IGF-1.

IGF-1R and IR show 48 % amino acid sequence homology [67]. Despite these similarities, the ligand-binding specificity is strict. The affinity for the IGF-1R is 1,000 times greater for IGF-1 than for insulin, and the IR has a 100-fold greater affinity for insulin as compared to IGF-1 [68]. Upon ligand binding, the IGF-1R dimerizes and undergoes auto-phosphorylation, leading to the activation of the insulin receptor substrate (IRS)-1 and IRS-2, with the latter being more preferentially activated by IGF-1 after interaction with its receptor [69, 70]. Given the high degree of homology, the insulin and IGF-1 half-receptors (composed of one α- and one β-subunit) can heterodimerize, leading to the formation of insulin/IGF-1 hybrid receptors (hybrid-Rs) which in many tissues are the most represented receptor subtypes [71–74]. The human IR exists in two isoforms (IR-A and IR-B), generated by alternative splicing of the insulin receptor gene that either excludes or includes 12 amino acid residues encoded by a small exon (exon 11) at the carboxyl terminus of the IR α-subunit. Predominant IR-A expression in cells coexpressing the IGF-1R leads to an increased formation of hybrid-Rs, which up-regulate the IGF system binding with high affinity by both IGF-1 and IGF-2, and activation of the IGF-1R pathway also after insulin binding [75]. In contrast, predominant IR-B expression leads to high-binding specificity whereby insulin activates only its own receptor and post-receptor signaling. Indeed, IR-B is the classical receptor for metabolic effects of insulin in muscle, liver and adipose tissues.

Growth hormone/IGF axis may play a role in maintaining glucose homeostasis in synergism with insulin. IGF-1R is expressed in skeletal muscle [76, 77] and IGF-1 was shown to promote glucose uptake in this tissue [78–83]. IGF-1 can directly stimulate glucose transport into the muscle through either IGF-1 or insulin/IGF-1 hybrid-R [84, 85], although this requires high concentrations of free IGF-1. The GH/IGF-1 axis may also affect lipid metabolism. Specifically, IGF-1 may have insulin-like effects in promoting the uptake of free fatty acids mainly in muscle, whereas at physiological concentration, IGF-1 does not exert direct effects on mature adipocytes. By contrast, GH has direct effects on mature adipocytes that result in stimulation of lipolysis with the release of free fatty acids following triglyceride breakdown [86]. Under physiologic conditions, therefore, it has been hypothesized that IGF-1 might influence glucose homeostasis largely through its insulin-like effects on muscle. After a meal, there is a significant increase in free IGF-1 via an insulin-induced suppression of IGFBP-1 secretion [68]. The IGFBP-1 gene is transcriptionally regulated by insulin; thus, the meal-induced increase in insulin leads to an increase in free IGF-1. This change may be adequate to stimulate fatty acid oxidation in muscle and suppress GH, and these changes may occur at physiologic IGF-1 levels.

GH/IGF-1 axis in diabetes mellitus

The GH/IGF-I axis is variably deranged in patients with diabetes mellitus. In type 1 diabetes, spontaneous and stimulated GH secretion is increased with reduced GH auto-feedback [87, 88] as effect of an impairment of somatostatin tone [89] likely due to a reduced GABA-ergic stimulation at the hypothalamic level [90]. Conversely, serum IGF-1 remains within the low range of healthy age-matched controls reflecting a state of hepatic GH

resistance, as already described in other clinical conditions such as renal and heart failure [11, 91], likely due to an insufficient portal delivery of insulin to the liver [92]. Indeed, in type 1 diabetes IGF-1 bioavailability is low because IGFBP-1 production by the liver is increased due to insulin deprivation. The low IGF-1 availability contributes to sustain the relative GH hypersecretion due to the lack of the feedback negative signal at the hypothalamus–pituitary axis [93]. In type 2 diabetes, chronic hyperglycemia in the presence of normal or increased insulin causes an increase in hypothalamic somatostatin tone with consequent impairment of GH secretion [94]. In this clinical context, IGF-1 values are variable in relationship with different degrees of insulin resistance and pancreatic beta cell dysfunction which reduce the ability of insulin to suppress IGFBP-1 synthesis by the liver [95].

Abnormalities of GH/IGF-1 axis in diabetes mellitus: clinical implications

The main challenge in the treatment of diabetes is represented by the prevention of microvascular and macrovascular complications in order to reduce morbidity, mortality, disability and costs [96]. For many years, a strict glycemic control has been considered the most important method to achieve sustained reduction in the occurrence of diabetic complications, even if recent intervention trials have given questionable results for macrovascular complications, especially when very tight diabetes control was pursued. HbA1c is usually used to estimate glycemic control, since this biomarker correlates very well with mean glucose levels. Intervention trials have shown that the closer HbA1c is to normal values, the better is the prevention of the microvascular complications. Even if the reduction of HbA1c to 7 % has been seen associated with a reduction in the development of macrovascular complications, an additional reduction in these complications was not achieved with a tighter glycemic control [96]. This suggests that other mechanisms and biomarkers should be taken into account in the prevention of macrovascular complications. Among them, post-prandial glycemia, glycemic variability, hypoglycemias, the so-called metabolic memory, other metabolic and vascular risk factors, such as lipids and hypertension which can play a major role [97, 98]. However, we hypothesize that also abnormalities of the GH/IGF-1 axis may play a role and that low-circulating IGF-1 may be an interesting marker of cardiovascular risk in type 2 diabetes.

In fact, low IGF-1 secretion and availability contribute to insulin resistance in diabetes [99], consistently with the experimental evidence that animals with the absence of liver-specific IGF-1 gene are characterized by hyperinsulinemia and skeletal muscle insulin resistance [100]. The mechanisms underlying the association between low IGF-1 and insulin resistance are largely unknown, but it could be hypothesized that the increase in GH secretion, consequent to the loss of IGF-1 feedback signal, may play an important role in favoring the persistence of insulin resistance [100]. Indeed, the augmented GH secretion, which occurs in patients with type 1 diabetes, may also contribute in the development of late diabetic complications, such as diabetic nephropathy and retinopathy [10, 11, 101]. This latter complication is also favored by the low IGF-1 synthesis and availability [102]. In fact, IGF-1 is essential for normal retinal vascular development and maintenance [103], and the hypoinsulinemia-induced IGF-1 deficiency of diabetes impairs pericyte replication, regeneration and survival with consequent loss of pericytes. This latter abnormality is the first morphological finding in diabetic retinopathy [104]. However, when serum IGF-1 values are restored by treatment of diabetes, neovascularization is favored and progression of retinopathy may occur [102].

IGF-1 was shown to exert mitogenic actions on vascular system, including stimulation of vascular smooth muscle cell proliferation and migration [105–107], which may prompt to the formation of atherosclerotic plaques supporting the hypothesis of a detrimental role of IGF-I in the development of cardiovascular disease [108]. More recently, however, the balance of experimental and clinical evidence appeared to contradict this view and several studies have clarified that IGF-1 may be instead a vascular protective factor, by several effects on the endothelial cells. In fact, IGF-1 stimulates nitric oxide production from endothelial cells, induces vasodilatation through the activation of potassium channels, with a consequent reduction in intracellular calcium [109], protects against plaque instability and ruptures by counteracting oxidized LDL-induced cytotoxicity and vascular smooth muscle cell apoptosis [108]. Consistently with these concepts, low-circulating IGF-1 has been associated with angiographically documented coronary artery disease [110, 111] and carotid intima-media thickness, a recognized surrogate marker for subclinical atherosclerosis [112]. This association was also demonstrated for patients with diabetes mellitus [108]. In patients with diabetes mellitus with a polymorphism in the promoter region of the IGF-1 gene creating an environment of chronic exposure to low IGF-1 levels, the risk of myocardial infarction was about threefold increased as compared to the patients harboring the wild-type allele [113]. Moreover, in patients with diabetes experiencing an acute myocardial infarction, high IGFBP-1, that is the expression of low IGF-1 availability, was shown to be associated with increased risk for cardiovascular mortality and morbidity [114]. Therefore, it is intriguing to hypothesize that one of the targets of the treatment of diabetes should be the normalization of

circulating IGF-1. As for GH-deficient subjects, an IGF-1 level in the low-normal range for age should probably be safely targeted [115]. In fact, also a sustained increase in circulating IGF-1 such as found in untreated acromegaly may be linked to not only increased oncological but even cardiovascular risk [116, 117].

Abnormalities of GH/IGF-1 axis in diabetes mellitus: effects of insulin therapy

It is still uncertain whether the metabolic control in diabetes may have per se an impact on the IGF system. In severely decompensated diabetes including diabetic ketoacidosis, plasma levels of IGF-1 were low [118]. By contrast, other studies did not demonstrate any significant correlation between HbA1c and IGF-1 [119–121].

Insulin delivery into the portal system is required to normalize IGF-1 synthesis and bioavailability. In fact, serum free IGF-1 tends to normalize rapidly after starting insulin therapy, whereas normalization of total IGF-1 was shown to require several weeks to occur [122]. Consistently with the concept that IGF-1 synthesis and bioavailability are influenced by intraportal insulin delivery, intraperitoneal insulin administration was shown to be more effective than subcutaneous route in normalizing the alterations of IGF-1 system in type 1 diabetes [121]. It is noteworthy that normalization of serum IGF-1, accompanied by a decrease in serum IGFBP-1, was shown to be closely correlated with the improvement of glucose homeostasis during insulin therapy providing evidence for the use of IGF-1 and IGFBP-1 as biomarkers of metabolic control in diabetes [123].

In addition to the effects on IGF synthesis and bioavailability, exogenous insulin may also activate IGF-1 signal in target tissues although, at physiological concentrations, little receptor cross talk occurs [124]. Another consequence of the structural homology of IR and IGF-1R is the formation of hybrid receptors which are highly expressed in patients with diabetes [125–130] and behave like full IGF-1R with regard to binding affinities for IGF-1 and insulin, as well as downstream signaling [131]. It is noteworthy that insulin analogs used in the clinical practice, such as insulin glargine, may have higher affinity for IGF-IR and hybrid receptors as compared to native insulin with potential promitogenic effects of these drugs [132, 133]. Preclinical studies showed that insulin glargine increases resistance to apoptosis in several tumor cell lines including colorectal, breast and prostate cancers [134], although the affinity of insulin analogs for IGF-1R was shown to be much lower than that of native IGF-1 [135]. The clinical relevance of these in vitro data is still uncertain. Although some studies reported an overall increased cancer risk associated with high doses of insulin glargine [136, 137], at the current time there is still inconclusive evidence to support the hypothesis that insulin glargine at physiological doses may increase the risk of tumors in clinical practice [138–140]. Notably, there are available new insulin analogs that, unlike insulin glargine, showed lower IGF-1R binding affinity and a low mitogenic/metabolic potency ratio [141–144].

Each insulin analog has an own affinity for IR, when compared to human "regular" insulin [145]. In addition, in vitro each analog has shown a specific affinity for IGF-1R and accordingly a different mitogenic power [145]. Insulin glargine in vitro showed an affinity for IGF-1R sixfold higher than that of human insulin, while other analogs had affinities for IGF-1R similar or even lower than those of the insulin reference. In addition, glargine showed in vitro a mitogenic power about eightfold greater than human insulin. Therefore, it has been hypothesized that glargine may increase cancer risk because of its IGF-1R affinity and mitogenic power. Really, several subsequent clinical studies did not confirm these data, and a specific large randomized controlled trial, designed to test cardiovascular and cancer risk of glargine, did not show any increase in cancer risk in patients treated with glargine [146]. This has been confirmed by other several large studies [147–149]. In particular, the use of glargine was not associated with either an increased mortality for cancer [147] or a higher incidence of malignancies [148, 149].

These results may be easily explained by the fact that after the subcutaneous administration of glargine, the real exposure to glargine is marginal, even at supra-therapeutic doses, as glargine is quickly processed to the so-called Metabolite 1 (M1), which mediates all metabolic effects of glargine [150]. There is another metabolite, called Metabolite 2 (M2), which is not virtually present in plasma. It is important to remember that both M1 and M2 have even lower binding to IGF-1R and less mitogenic potential when compared to human "regular" insulin [151].

Therefore, it is unlikely that glargine U100 or U300 (slow release from injection site depot) or other insulins such as detemir or degludec (acylated insulin and plasma albumin bound based mechanism of action) or human insulin [152] can increase in vivo mitogenesis. However, two considerations should be made: All insulins can exert an action on IGF-1R, albeit with different affinities, and this effect may be even positive. Indeed, it may promote all effects of IGF-1 that are decreased in diabetes. Therefore, therapy in diabetes with insulin with high affinity for the IGF-1R may exert a cardioprotective effect by restoring the right level of IGF-1 in bloodstream and target tissues, whereas insulins with low affinity for the IGF-1R may lack this

positive effect. Furthermore, an excessive and indirect stimulation of IGF-1R due to sustained and chronic hyperinsulinemia (therefore likely not due to a specific insulin), over the therapeutic level required to overtake an acute/chronic insulin resistance status (what we can call the "individual critical threshold"), may be deleterious as it may increase the cardiovascular risk in the short and medium term and mitogenic/proliferative action in the long term.

Treatment of diabetes with IGF-1

Exogenous IGF-1 administration was shown to reduce serum glucose levels in healthy individuals as well as in patients with insulin resistance, type 1 and type 2 diabetes [78, 82, 153–163]. Interestingly, IGF-1-induced reduction in serum glucose levels was accompanied by an improvement in insulin sensitivity [156, 162, 163]. These studies provide indirect evidence that relatively high endogenous levels of IGF-1 may reduce insulin resistance and, thereby, lower the risk of type 2 diabetes. The predominant effect of IGF-1 on carbohydrate metabolism seems to be secondary to its effects on lipid metabolism. Because suppression of insulin and GH secretion occurs at pharmacologic levels of IGF-1, it is difficult to extrapolate from the results of most published studies and conclude that these effects can occur at normal physiologic levels. However, GH suppression would be expected to lead to decreased free fatty acid flux in liver and reduced antagonism of insulin action on gluconeogenesis [68].

Although most of the effects of IGF-1 on glucose homeostasis are mediated by its action on IR pathways, there is also evidence that IGF-1 may directly act on the endocrine pancreas variably influencing β-cells survival, replication and hormonal synthesis as well as suppressing glucagon [164–175]. Several attempts of administration of IGF-1 in patients with diabetes have been made, both in type 1 and type 2 diabetes, with the aim of a metabolic improvement of the disease. In general, in type 1 diabetes HbA1c was improved and insulin requirements were decreased accompanied by an enhanced insulin sensitivity, the latter effect due to the action of IGF-1 per se rather than by the reduction of GH values [176–178]. In type 2 diabetes, IGF-1 administration enhanced insulin sensitivity with decreases in glucose, endogenous insulin, C-peptide secretion and, in some cases, an improved area under the curve after oral glucose administration [160, 179, 180]. As most of the patients studied were obese with low GH concentrations, it is highly likely that the enhanced insulin sensitivity was caused by an effect on free fatty acid metabolism in muscle and by a suppression of renal gluconeogenesis and not simply by suppression of GH secretion [68].

Perspectives

The GH/IGF-1 axis is regulated in a complex manner by the metabolic alterations occurring in diabetes mellitus and is very sensitive to changes in endocrine milieu determined by insulin treatment. Particularly, in decompensated diabetes, IGF-1 levels are low and insulin administration may have beneficial effects by acting at the IGF-1R level. Different affinities for this latter receptor may lead to variable degrees of IGF-1 restoration with different insulin preparations. From lessons learned in GHD and acromegaly patients [115–117], we now know that both very low and high IGF-1 levels are related to increased cardiovascular risk. Therefore, insulin may be considered an endocrine pacer of the GH/IGF-1 axis in diabetes and restored-to-normal IGF-1 may be hypothesized to be a good marker of appropriate insulin treatment of the subject and may integrate and make more robust the message coming from HbA1c in terms of prediction of cardiovascular risk. We expect that in near future, a diabetes clinical research focus will challenge the superiority or non-inferiority of new insulin analogs and of their biosimilars, back-grounding on their specific mechanism of action [149], on combined biochemical end points including HbA1c, GH and IGF-1 in each personalized treatment at same fixed stage points. In fact, we need to focus on the concept that exogenous insulins or incretins, directly or indirectly, may exert their either metabolic or proliferative effects with different magnitude, and therefore act as either endocrine pacers or disruptors, in the same people with diabetes who during their lifecycle physiologically undergo relevant changes in the hormonal status [181]. A new era in the approach to monitoring diabetes treatment can start not only by measuring HBA1c or glucose circadian fluctuations [182, 183] but also by evaluating the impact of personalized treatment of diabetes on the ancestral balance between metabolic and proliferative effect of the integrated system constituted by insulin, GH and IGF-1 in the circulation and at the tissue level.

Conflict of interest A. Giustina, R. Berardelli, C. Gazzaruso and G. Mazziotti declare that they have no conflict of interest.

Human and animal rights disclosure This article does not contain any studies with human or animal subjects performed by the any of the authors.

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