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Review

Insulin resistance of amino acid and protein metabolism in type 2 diabetes☆

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SUMMARY

Although insulin resistance in T2DM (type 2 diabetes mellitus) is usually referred to glucose and lipid metabolism, the question whether such a resistance affects also amino acid and protein metabolism is both relevant and not easy to be answered. Available data indicate a reduced response to insulin in the inhibition of proteolysis at low, near basal hormone levels, whereas such a response appears to be normal at high physiological doses. In most studies in T2DM subjects the stimulation of whole-body protein synthesis in the presence of hyperinsulinemia and euaminoacidemia appears to be normal, although one single study reported lower rates in male T2DM subjects with obesity. The response to insulin of plasma protein synthesis (albumin and fibrinogen) is also normal. However, some metabolic steps of amino acids related to vascular complications (methionine and arginine) exhibit a defective response to insulin in T2DM subjects with nephropathy. In summary, although gross alterations in the response of whole-body protein turnover are not evident in T2DM, specific investigations reveal subtle abnormalities in metabolic steps of selected amino acids. Furthermore, the effects of interaction between diabetes (with the associated insulin resistance) and older age in the pathogenesis of sarcopenia in the elderly deserve more specific studies.

Resistance to the insulin-induced stimulation of glucose disposal and suppression of endogenous glucose production is a widespread finding in type 2 diabetes mellitus (T2DM). Skeletal muscle is the major site of the resistance to insulin-stimulated glucose uptake, where glucose is taken up at a ≈50% lower rate than in healthy controls.[1] Such a resistance, in conjunction with a relative or absolute defect in insulin secretion,[2] is the key event in the abnormal glucose regulation in T2DM.

Insulin however affects not only glucose metabolism, but also a number of others metabolic pathways related to lipids and amino acids (Table 1). Therefore, in insulin-resistant conditions such as T2DM, this resistance could theoretically be extended beyond glucose metabolism. As regards lipid metabolism, a resistance has been clearly demonstrated in T2DM,[3–5] involving mainly the inhibition by insulin of lipolysis, which on turn could contribute to the increased fat deposition in insulin-sensitive tissues as well as to lipotoxicity. In contrast, its existence with respect to amino acid and protein metabolism in T2DM has been less studied and is still somehow controversial, despite the fact that amino acid and protein metabolism are highly influenced by insulin.[6,7] This review will present and discuss data on insulin resistance affecting the metabolism of nitrogen compounds in type 2 diabetes mellitus.

Generally speaking, a resistance to the effect of insulin on amino acid and protein metabolism in T2DM could either be irrelevant and difficult to demonstrate, or, alternatively, be translated into some clinically and instrumentally measurable alterations. In this case, defects in the regulation by insulin of protein metabolism in T2DM may lead to changes in body tissue composition, metabolic rates, individual amino acid metabolic steps, etc. Clinical evidence supports either of these two possibilities. Although appreciable changes in any of the above mentioned issues are usually not readily apparent in otherwise healthy, well nourished and physically active T2DM subjects, a more in depth data analysis reveals a number of subtle and multi-faceted alterations which could retain a pathophysiological impact. Furthermore, these alterations may interact with age, dietary and lifestyle habits (physical activity, smoke, environmental factors), as well as with pharmacological treatments, to produce appreciable changes on amino acid and protein metabolism. Therefore, these additional factors should be taken into account and selectively considered in this context.

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Table 1
Known sites/effects of insulin resistance on glucose and lipid metabolism in T2DM.

- Impaired glucose disposal
- Reduced glycogen synthesis
- Impaired suppression of HGP
- Increased (defective suppression of) gluconeogenesis
- Impaired suppression of lipolysis
- Defective suppression of lipoprotein production

HGP: Hepatic glucose production.

1. Body composition

Besides the well known role and presence of abnormal fat distribution, metabolism and regulation in T2DM,[5] proofs of the existence of altered protein composition in T2DM are limited. Protein wasting is usually uncommon, and body protein composition doesn't seem to be consistently altered in either young or middle-age T2DM diabetic subjects without coexisting protein wasting conditions.[8] In contrast, an excessive loss of skeletal muscle mass[9] has been reported in elderly people with diabetes, although also an increase in midthigh skeletal muscle areas has been described in obese subjects either with or without diabetes.[10] Elderly subjects may exhibit an age-associated sarcopenia which can be enhanced by the presence of diabetes itself, as recently reported.[11] Interestingly, these differences have been found also in middle-aged and elderly women with diabetes, as compared with non diabetic, BMI- and age-matched women.[11] It is well established that with ageing, skeletal muscle becomes infiltrated with fat, which may itself determine insulin resistance.[12] The interaction between muscle fat and insulin sensitivity however is not so simple, since the amount of muscle fat did not correlate with either insulin resistance or muscle mitochondrial function, in T2DM subjects following a training program.[13]

2. Protein degradation and synthesis in T2DM, and the effects of insulin

A large body of data have been generated, in T2DM, on the effects of insulin on the regulation of amino acid and protein kinetics, including relationships between circulating insulin concentrations and protein turnover (degradation and synthesis).[14–26] The general scheme of the investigations was of two types. A first group of data reports estimates of protein turnover at the "spontaneous" basal (or at only modestly increased) insulin concentrations (i.e. about 2–4 times greater than "normal" basal values), as those following an intensive insulin treatment[14–25] (Table 2, group A data). Alternatively, another set of data has been generated before and following an exogenous insulin infusion attaining upper-physiological hormone concentrations with glucose clamp, either with or without amino acid clamp[17,19,20,25,26] (Table 2, Group B data). Protein turnover was traced mainly with leucine,[14,15,17–20,26] but also with phenylalanine,[16,24,25] tyrosine,[24] methionine,[20] or glycine[22,23] isotopes.

The first group of studies[14–25] are pretty concordant in reporting either the need for a greater insulin concentrations in T2DM than in healthy controls, to maintain the same rate of protein degradation, or a reduced/absent effect in T2DM by the (modestly increased) concentrations of insulin, to suppress protein degradation to rates comparable to those in controls (Table 2, Group A data). This was observed by our research group too, by using leucine, methionine and phenylalanine tracers (Fig. 1).[16,19,20] The suppression of arginine flux, although it is not an essential aminoacid, paralleled that of the essential ones (27). These findings therefore agree about a reduced effect of the prevailing insulin concentrations (in this case, at low, near basal levels) in suppressing endogenous protein degradation, or, alternatively, in maintaining it within "normal" ranges proportional to the insulin levels.

In contrast, the second group of data lead to opposite conclusion in most instances. At higher insulin concentrations raised to the upper-physiological range, i.e. to 600-1000 pmol/L with glucose clamp, either with or without an isoaminoacidemic clamp, endogenous protein degradation was suppressed to an extent similar to that observed in controls (Table 2, Group B data). Thus, under these conditions, no resistance was observed. Taken together, it can be concluded that, if a resistance is present, it is limited to the lower ranges of insulin levels, but it disappears at higher hormone concentrations.

As anticipated, in some of the above mentioned studies, whole-body protein synthesis was also determined. A stimulation of whole-body protein synthesis is usually detected, in both healthy subjects and patients with T2DM, under hyperaminoacidemic conditions, either with or without hyperinsulinemia,[17,28,29] whereas insulin alone decreases (or at least it doesn't change) whole-body protein synthesis.[6,17,28,29] The reasons for the (apparent) failure by insulin itself to increase whole-body protein synthesis is a classic issue for debate, and they have extensively been discussed elsewhere.[6] They

Table 2
Published data on the effect of insulin to inhibit proteolysis in T2DM.

Author & date	Experimental design	Isotope used	WB proteolysis
Reduced or no effect [at "basal" or modestly increased (140-200 pmol/L)] insulin concentration (Group A data)			
Staten (1986)	Basal state, following insulin therapy	^{13}C,^{15}N-leucine	No change
Umpleby (1990)	Poorly controlled T2DM subjects	^{14}C-leucine	No difference vs. controls
Welle (1990)	Basal state, following insulin therapy	^{13}C-leucine	No change
Biolo (1992)	Basal state, 2× greater insulin than in controls	^{3}H-phenylalanine	No difference vs. controls
Luzi (1993)	Basal state,greater insulin than in controls	^{14}C-leucine	No difference vs. controls
Gougeon (1994)	Isoenergetic diet	^{15}N-glycine/urinary ^{15}N-urea	Greater than in controls
Denne (1995)	Basal state, intensified insulin therapy	$^{2}H_5$−phenylalanine	No change
Gougeon (2000)	Low energy diet	^{15}N-glycine/urinary ^{15}N-urea	No difference vs. controls
Halvatsiotis (2002a)	Basal state, 4× greater insulin than in controls	^{13}C-leucine	No difference vs. controls
Halvatsiotis (2002b)	Basal state & intensified insulin therapy (vs. controls)	^{15}N-phenylalanine, $^{2}H_4$−tyrosine	No difference vs. controls
Barazzoni (2003)	Basal state, modestly greater insulin than in controls	$^{2}H_3$-leucine	No difference vs. controls
Tessari (2005)	Basal state, modestly greater insulin than in controls	^{13}C; $^{2}H_3$-methionine, $^{2}H_3$-leucine	No difference vs. controls
Normal effect at "clamp", high physiological (600-1000 pmol/L) insulin concentration (Group B data)			
Luzi (1993)	Euglucemic, hyperaminoacidemic hyperinsulinemia	^{14}C-leucine	Normal suppression
Denne (1995)	Euglucemic, hypoaminoacidemic hyperinsulinemia	$^{2}H_5$−phenylalanine	Normal suppression
Barazzoni (2003)	Euglucemic, isoaminoacidemic hyperinsulinemia	$^{2}H_3$-leucine	Normal suppression
Tessari (2005)	Euglucemic, hypoaminoacidemic hyperinsulinemia	^{13}C; $^{2}H_3$-methionine, $^{2}H_3$-leucine	Normal suppression
Pereira (2008)	Euglucemic, isoaminoacidemic hyperinsulinemia	^{13}C-leucine	Normal suppression