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Letters

Comments

-to: Charlton R, Smith G, Day A (2001) Munchausen's syndrome manifesting as factitious hypoglycaemia. Diabetologia 44: 784–785

To the Editor: I read with interest the *Observations* of Drs. Charlton, Smith and Day in your June issue [1] about factitious hypoglycaemia. The authors searched and reviewed literature between 1966 and 1999 using Medline. They further state that they had identified 46 papers, containing 69 case reports, with a range of one to four case reports in each paper. I have to assume, therefore, that they inadvertently omitted our paper [2] which reported the largest number (10) of patients with surreptitious hypoglycaemia along with the longest follow-up (15 years). In our 1988 report, we divided patients presenting with factitious hypoglycaemia into two groups (five in each category): those who were not known previously to take insulin and those in whom use of insulin had been sanctioned by the medical profession. We outlined the difficulty of making and confirming the diagnosis, the prevalence of women (90%) with knowledge of the medical profession and the poor long-term prognosis of the majority of those patients (only three made a successful transition to a productive life after the diagnosis of factitious hypoglycaemia was established). These are essentially the same points now made by Charlton et al.

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References

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-to: T. Skoog et al. (2001) Tumour necrosis factor-α (TNF-α) polymorphisms *–857C/A* and *–863C/A* are associated with TNF-α secretion from human adipose tissue. Diabetologia 44: 654–655

To the Editor: Skoog et al. have recently described that the secretion of TNF-α from adipose tissue varied among non-obese subjects according to the *TNF-α –863C/A* polymorphism [1]. Adipose tissue from subjects with the rare allele *–863/A* secreted less TNF-α than adipose tissue from non-obese subjects carrying the *–863C* allele. This indicated that *C* to *A* substitution at position *–863* represents a functional polymorphism, which leads to decreased *TNF-α* gene expression and thereby less production and secretion of the cytokine [1]. We have described that the *TNF-α –308G/A* polymorphism was associated, in parallel to constitutively different transcription rates of the cytokine, with increased body fat and insulin resistance [2]. We investigated whether the pattern of TNF-α secretion attributed to *TNF-α 863C/A* was also linked to a different insulin action.

We studied 28 consecutive healthy subjects. Six of them carried the *–863A* allele and 22 were homozygotes for the *–863C* allele (allele frequency 0.21/0.79, distribution in Hardy-Weinberg equilibrium). The two groups were similar in age, BMI and gender distribution (Table 1). The insulin sensitivity index (frequently sampled intravenous glucose tolerance test with minimal model analysis) was higher in *–863A* subjects than in

Table 1. Anthropometric and biochemical variables of the study subjects

Variable	C/C	C/A	P
n	22	6	–
Men/women	11/11	3/3	NS
Age (years)	34 ± 8	38 ± 6	NS
Body mass index (kg/m^2)	32.1 ± 3.1	30.9 ± 2.8	NS
Waist-to-hip ratio			
Men	1.00 ± 0.03	1.03 ± 0.06	NS
Women	0.98 ± 0.06	0.97 ± 0.08	NS
Fasting glucose (mmol/l)	5.64 ± 0.9	4.92 ± 0.43	0.09
Fasting insulin (mU/l)	13.3 ± 7.1	9.7 ± 6.0	NS
HbA_{1c} (%)	5.2 ± 0.6	4.7 ± 0.29	0.07
Insulin sensitivity (min^{-1}/mU/l)	1.54 ± 1.1	2.03 ± 0.5	0.028
Cholesterol (mmol/l)	5.42 ± 0.8	4.56 ± 0.62	0.07
LDL-cholesterol (mmol/l)	3.8 ± 0.8	3.19 ± 0.62	0.1
HDL-cholesterol (mmol/l)	1.01 ± 0.15	1.09 ± 0.33	NS
Fasting triglycerides (mmol/l)	1.69 ± 0.7	1.03 ± 0.5	0.021
Serum TNF-α (pg/ml)	22.6 ± 10	24.1 ± 10	NS
Serum sTNFR-2 (ng/ml)	3.1 ± 0.3	2.6 ± 0.3	0.04

sTNFR2, soluble fraction of the TNF-α receptor-2

the *–863C* homozygote subjects. Fasting serum glucose and glycosylated haemoglobin tended to be lower in *–863A* carriers than in *–863C* allele homozygote subjects. Fasting serum triglycerides were lower, whereas total and LDL-cholesterol tended to be lower in the *–863A* carriers (Table 1). Serum TNF-α was not different between the groups but serum concentration of the soluble fraction of the TNF-α receptor-2 (sTNFR2) was lower in the *–863A* carriers. All these measurements were carried out as described previously [2, 3]. These findings suggest that the different adipocyte secretion rates of TNF-α according to *–863C/A TNF*-α gene polymorphism are mirrored by insulin action, at least in moderately obese subjects. As TNF-α probably plays a paracrine and autocrine function, peripheral TNF-α values do not reflect its integrated action. The latter is probably indicated by sTNFR2 concentration, as previously reported [3].

Skoog et al. reported that the secretion of TNF-α from adipose tissue of obese subjects did not differ between carriers and non-carriers of the *A*-allele [1]. However, in the obese group the mean BMI ± SEM was 40.0 ± 0.7, indicating the inclusion of some morbid obese subjects. Some associations among obesity, obesity-associated phenotypes and cytokines have been found to be most pronounced in subjects who are not morbidly obese [4]. Enhanced activity of cytokines caused by the development of obesity is predicted to contribute to the development of obesity-associated phenotypes but is also expected to limit the progression of obesity. These mechanistic relationships are probably lost in subjects with morbid obesity. The inclusion of subjects with morbid obesity might lead to false-negative associations when evaluating *TNF*-α *–308G/A* polymorphism and obesity phenotypes [5] in contrast to the studies that have not included them [2, 4] or that have evaluated a small proportion of these subjects [6].

Obesity is a multifactorial condition caused by multiple genes. The *TNF*-α gene seems to be a strong candidate for obesity and for obesity-associated phenotypes, including insulin resistance and dyslipidaemia. Indeed, lipid alterations are interrelated with the activity of the TNF-α axis and insulin action, even in healthy volunteers (Table 1) [7].

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