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Original contribution

Intramyocellular lipid content in subjects with impaired fasting glucose after telmisartan treatment, a randomised cross-over trial

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ABSTRACT

Ectopic lipid accumulation in skeletal muscle is associated with insulin resistance. Telmisartan improves metabolic parameters in type 2 diabetic patients. The aim of our study was to evaluate the in vivo effect of telmisartan on intramyocellular lipid content (IMCL) in subjects with impaired fasting glucose (IFG) by magnetic resonance spectroscopy (MRS). We enrolled 10 subjects with IFG in a cross-over, placebo-controlled, randomized, double-blind trial, treated with 3 weeks of telmisartan (160 mg daily) or placebo. After completing each treatment, a hyperinsulinaemic euglycaemic clamp (1 mU/kg per min; 5 mmol/l; 120 min) to assess insulin action (metabolic clearance rate of glucose, MCR) and ^{1}H MRS of the m. tibialis anterior using a MR Scanner Siemens Vision operating at 1.5 T to evaluate IMCL content, were performed. Plasma adipokine levels were determined simultaneously. Telmisartan treatment resulted in a lower fasting plasma glucose (FPG) ($p < 0.05$), but insulin action was comparable to after placebo. Telmisartan did not affect IMCL content. After placebo, IMCL correlated negatively with total cholesterol ($p < 0.001$), MCR ($p < 0.05$) and adiponectin ($p < 0.05$) and positively with FPG ($p < 0.05$). After telmisartan treatment there was only a positive correlation between IMCL and TNFα ($p < 0.05$). IMCL content is related to parameters of glucose metabolism and insulin action in sedentary IFG subjects. A short telmisartan treatment did not affect the IMCL content despite its positive effect on FPG. The improvement in FPG was probably mediated through interference with other metabolic pathways.

1. Introduction

The development of insulin resistance and diabetes is accompanied by ectopic lipid accumulation. Skeletal muscle is one of the principal targets of insulin action, and is a typical site of ectopic fat accumulation. The muscle tissue contains two lipid compartments formed by triglycerides (TAG). One contains lipids stored in droplets in close contact with mitochondria within the cytoplasm of muscle cells (intramyocellular lipids, IMCL). The other compartment is formed by lipids located along muscle fibres within adipocytes (extramyocellular lipids, EMCL). IMCL serve as an energy store for mitochondrial aerobic metabolism that is readily accessible during long-term exercise. Distinguishing between these two compartments is not always possible using classical invasive methods such as muscle biopsies except using histochemistry or electron microscopy. However, proton nuclear magnetic resonance spectroscopy (^{1}H MRS) at a field strength of 1.5 T or higher is a noninvasive method that enables the separation and quantification of the IMCL and EMCL signals (the CH_3 and CH_2 signals of intramyocellular and extramyocellular lipids, respectively) in muscle tissue [1,2]. Results from ^{1}H MRS have also been shown to be in good agreement with those obtained from muscle biopsies and electron microscopy [3,4].

The precise mechanism responsible for ectopic lipid accumulation is unknown but could be explained by a dysfunction in the subcutaneous adipose tissue. High lipid supply exceeds the mitochondrial oxidative capacity in skeletal muscle cells and IMCL accumulation follows. IMCL content assessed by ^{1}H MRS is associated with insulin resistance and type 2 diabetes (T2DM). Interestingly, the relationship between IMCL content and insulin resistance exists even in first-degree relatives of T2DM patients [5,6] and healthy subjects [7]. Paradoxically, insulin sensitive trained endurance athletes with high energy demands also display high IMCL contents [8]. The mitochondrial oxidative capacity, which is low in diabetics and high in athletes, probably results in the difference between the insulin resistant and sensitive states [9,10].

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Telmisartan is an angiotensin receptor blocker (ARB). The positive effect of blocking the renin-angiotensine-aldosteron system (RAS) on insulin sensitivity has already been reported [11,12]. All components of the RAS are expressed in adipose tissue, and inhibition of the system stimulates adipogenesis [13]. Mature adipocytes are able to store excess fat and thereby prevent ectopic fat accumulation. Telmisartan can also partially modulate peroxisome proliferator-activated receptor gamma (PPARγ), which is a nuclear transcription factor and regulates the expression of multiple genes involved in the intermediary metabolism of glucose and lipids and thus positively affects insulin sensitivity. PPARγ is mostly expressed in adipose tissue and only sparsely in skeletal muscle. Its stimulation is essential for the differentiation of adipocytes, and it promotes lipid storage in adipose tissue and thereby also prevents ectopic lipid accumulation [14].

We have already examined the effect of telmisartan on insulin sensitivity and the insulin stimulated adipokine profile in subjects with impaired fasting glucose (IFG) [15]. The main outcome of that study was that there is a reduction in fasting plasma glucose (FPG) after telmisartan treatment, which is also in agreement with a meta-analysis on the effect of telmisartan on insulin sensitivity [16]. The aim of this current study was to evaluate the effect of telmisartan on ectopic lipid accumulation in skeletal muscle (m. tibialis anterior) in subjects with IFG. We lack information about the effect of telmisartan on IMCL content, and the question has so far not been studied in this specific group of subjects. We hypothesised that a positive effect of telmisartan on fasting plasma glucose, mediated either through RAS inhibition or PPARγ activation, might be reflected in a reduction in IMCL content.

2. Methods

2.1. Subjects

We enrolled 10 male patients with metabolic syndrome defined according to the NCEP-ATPIII criteria, revised in 2005 [17]. Out of 12 subjects taking part in the original study, 2 subjects were not investigated by MRS due to contraindications. Impaired fasting glucose confirmed by an oral glucose tolerance test was an obligate criterion for enrolment in the study. One patient had both impaired fasting glucose and impaired glucose tolerance. Only male subjects participated in the study to exclude the variability in insulin sensitivity of women during the menstrual cycle and sexual dimorphism in adipokines. All subjects had a sedentary life style. Patients were tested for common metabolic and anthropometric characteristics, listed in Table 1. Patients enrolled in the study were treatment-naive with regard to oral antidiabetic medications. Antihypertensive treatment was adjusted during the 4-week run-in period as follows: angiotensin-converting enzyme and ARB treatment was halted and replaced by a metabolically neutral calcium channel blocker (if required), with a stable dose during the whole study. None of the patients had their dietary intake of salt or protein restricted. Patients with overt diabetes (diagnosed by an oral glucose tolerance test), an inflammatory or other major organ disease were excluded from the study. All subjects gave their informed consent with the study protocol, which had been reviewed and approved by the local ethics committee. The study was performed in accordance with the Helsinki Declaration and Title 45, Code of Federal Regulations, Part 46, Protection of Human Subjects. The EudraCT number 2006-000490-29 had been issued for our Sponsor's Protocol Code No. 1, 1.1.2006.

Table 1
Characteristics of the study group.

n	10
Age (years)	49.5 ± 6.1
BMI (kg/m2)	29.3 ± 4.37
Waist (cm)	103.9 ± 8.2
Systolic blood pressure (mmHg)	134.0 ± 12.6
Diastolic blood pressure (mmHg)	90.0 ± 10.8
HbA1c (%)	3.78 ± 0.36
Total cholesterol (mmol/l)	5.70 ± 0.93
HDL cholesterol (mmol/l)	0.99 ± 0.12
LDL cholesterol (mmol/l)	3.61 ± 0.91
Serum triglycerides (mmol/l)	2.55 ± 1.56
Plasma glucose 0 min, oGTT (mmol/l)	6.08 ± 0.36
Plasma glucose 120 min, oGTT (mmol/l)	6.90 ± 2.0

Abbreviations: BMI, body mass index; HbA1c, glycosylated haemoglobin; oGTT, oral glucose tolerance test.

2.2. Study protocol

The study was a randomized, placebo-controlled, double-blind, crossover trial consisting of two treatment sequences. After a 4-week run-in period, the subjects were randomly assigned to receive 160mg telmisartan daily (Micardis 80 mg; Boehringer Ingelheim Pharma GmbH, Ingelheim am Rhein, Germany) or placebo for 3 weeks. After a 2-week washout period, the patient groups switched treatments (telmisartan or placebo) and continued for another 3 weeks. Randomization was performed by a standard procedure. The code was not broken until all data were entered into a database, which was locked for editing. Drug compliance was assessed by the effect on blood pressure and by study drug accountability. Patients were instructed to adhere to their ordinary lifestyle and avoid changes in food intake, alcohol consumption and exercise during the whole study duration. At the end of each 3-week treatment period with telmisartan or placebo, all patients underwent a ^{1}H MRS of the musculus tibialis anterior followed the next day by a 2-hour hyperinsulinemic euglycemic clamp (HEC) combined with indirect calorimetry. No side effects of telmisartan were recorded.

2.2.1. Hyperinsulinemic euglycemic clamp

Subjects were examined on an outpatient basis after an 8–10 h overnight fast with only tap water allowed ad libitum. The HEC, lasting 2 hours, was conducted as described earlier [18]. Briefly, two indwelling catheters were inserted, one into an antecubital vein in the right arm for infusions of insulin and glucose and another into a wrist vein for sampling of arterialized venous blood (the hand was placed in a heated box at 65 °C). The rate of the continuous insulin infusion (Actrapid HM, NovoNordisk, Copenhagen, Denmark) was 1 mU/kg per min (resulting in constant hyperinsulinemia of approximately 75 μU/ml), and the rate of the 15% glucose infusion was adjusted to maintain fasting levels (about 5 mmol/l) based on plasma glucose measurements that were performed every 5 min from arterialized venous blood. To prevent hypokalemia during insulin infusion, potassium chloride was added to the 15% glucose infusion (30 mmol KCl/l of glucose). Before the clamp, fasting plasma glucose levels were checked, and the clamp procedure was started when concentrations dropped to lower than 6 mmol/l. No glucose was infused until plasma glucose had declined to the clamp-target level.

2.2.2. Indirect calorimetry

Substrate utilization and energy expenditure were assessed by indirect calorimetry [19]. Gas exchange measurements were performed during a 45 min basal period before starting the insulin infusion and during the last 45 min period of the clamp. A transparent plastic ventilated hood was placed over the subject's head and made airtight around the neck. Slight negative pressure was maintained in the hood to avoid the loss of expired air. A constant fraction of air flowing out of the hood was automatically collected for analysis.