**The effects of recombinant human insulin‑like growth factor-1/insulin‑like growth factor binding protein‑3 administration on lipid and carbohydrate metabolism in recreational athletes**

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**ABSTRACT**

**Objective:** Previous studies suggested that recombinant human IGF-1 (rhIGF-1) administration affects carbohydrate and lipid metabolism in healthy people and in people with diabetes. This study aimed to determine the effects of rhIGF-1/rhIGF binding protein‑3 (rhIGFBP‑3) administration on glucose homeostasis and lipid metabolism in healthy recreational athletes.

**Design and Setting:** Randomised, double‑blind, placebo‑controlled rhIGF-1/rhIGFBP‑3 administration study at Southampton General Hospital, UK.

**Participants:** 56 recreational athletes (30 men, 26 women)

**Methods:** Participants were randomly assigned to receive placebo, low dose rhIGF‑1/rhIGFBP‑3 (30 mg/day) or high dose rhIGF-1/rhIGFBP‑3 (60 mg/day) for 28 days. The following variables were measured before and immediately after the treatment period: fasting lipids, glucose, insulin, C‑peptide and glycated haemoglobin. The homeostatic model assessment (HOMA‑IR) was used to estimate insulin sensitivity and indirect calorimetry to assess substrate oxidation rates. The General Linear Model approach was used to compare treatment group changes with the placebo group.

**Results:** Compared with the placebo group, there was a significant reduction in fasting triglycerides in participants treated with high dose rhIGF‑1/rhIGFBP‑3 (*P* = 0.030), but not in the low dose group (*P* = 0.390). In women, but not in men, there were significant increases in total cholesterol (*P* = 0.003), HDL cholesterol (*P* = 0.001) and LDL cholesterol (*P* = 0.008). These lipid changes were associated with reduced fasting insulin (*P* = 0.010), C‑peptide (*P* = 0.001) and HOMA‑IR (*P* = 0.018) in women, and reduced C‑peptide (*P* = 0.046) in men.

**Conclusions:** rhIGF-1/rhIGFBP‑3 administration for 28 days reduced insulin concentration, improved insulin sensitivity and had significant effects on lipid profile including decreased fasting triglycerides.

**INTRODUCTION**

Insulin‑like growth factor-1 (IGF-1), growth hormone (GH) and insulin initiate complex metabolic responses to nutrient intake, and IGF-1 provides a mechanism for coordinating energy metabolism in different tissues.[1](#_ENREF_1) Previous studies have investigated the effects of recombinant human IGF-1 (rhIGF-1) administration on lipoprotein metabolism and lipid profiles in small populations of healthy men.[2](#_ENREF_2) Furthermore, it has been shown that IGF-1 treatment has beneficial effects on glycaemic control in people with diabetes.[3](#_ENREF_3) Recombinant human IGF-1 (rhIGF-1) administration improved insulin sensitivity and decreased HbA1c in people with type 1 and type 2 diabetes.[4](#_ENREF_4),[5](#_ENREF_5) Some adverse effects have been associated with the use of rhIGF-1, including hypoglycaemia, seizures and jaw pain.[3](#_ENREF_3) There were also concerns that increased serum IGF-1 concentration was associated with progression of retinopathy in the short-term.[6](#_ENREF_6) Longer term administration of rhIGF-1, however, was not associated with worsening of diabetes-related complications.[7](#_ENREF_7)

Mecasermin rinfabate (iPLEXTM) is a recombinant protein complex of rhIGF-1 and rhIGF binding protein‑3 (rhIGFBP‑3), combined non‑covalently in equimolar proportions. It was developed to prolong the circulating half‑life of IGF-1 and to reduce the potential side‑effects of administration.[8](#_ENREF_8) We previously reported the results of a randomised, double-blind, placebo‑controlled study designed to detect changes in serum biomarkers in response to administration of this complex.[9](#_ENREF_9) A further aim of the study, reported here, was to investigate the effects of rhIGF-1/rhIGFBP‑3 administration over a 28‑day period on lipid and carbohydrate metabolism in healthy recreational athletes.

**MATERIALS AND METHODS**

**Setting and Participants**

The study was performed at the Wellcome Trust Clinical Research Facility (WTCRF), Southampton General Hospital, Southampton, UK. The study received ethics approval from the Southampton and South West Hampshire Research Ethics Committee (06/Q1702l50) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was regulated by the Research and Development Office of University Hospital Southampton NHS Trust. The study was not defined as a Clinical Trial because the Medicines and Healthcare Products Regulatory Agency (MHRA, UK) did not classify the rhIGF‑1/rhIGFBP‑3 complex in the context of this study as an Investigational Medicinal Product.

Fifty‑six healthy recreational athletes (30 men, 26 women) aged between 18 and 30 years, who engaged in regular physical activity (two or more sessions per week), were recruited by poster advertisement at the University of Southampton Faculty of Medicine and University of Southampton sports centres. Participants were ineligible if they were competing at elite level, had a history of using performance‑enhancing drugs or if they were found to be anaemic at the time of screening. Anyone with previous history of endocrinopathy, diabetes mellitus or neoplastic disease was excluded. Pregnant women were not allowed to participate; pregnancy tests were performed on all female volunteers prior to enrolment and they were advised to use safe contraception for the duration of the study if sexually active. All participants provided written informed consent.

**Baseline assessments**

Participants attended the WTCRF, Southampton General Hospital at 9am after a 12‑hour overnight fast. Participants did not exercise on the morning of the assessment. An intravenous cannula was inserted into an antecubital vein and fasting venous blood samples were collected for glucose, insulin, C­peptide, non­esterified fatty acids (NEFA), glycerol, triglycerides, total cholesterol, HDL‑cholesterol, LDL-cholesterol and glycated haemoglobin (HbA1c). After resting in a recumbent position for 15 minutes, indirect calorimetry was performed using the Deltatrac II™ metabolic cart (Datex­Engstrom Corp., Helsinki, Finland). Participants lay supine for 20 minutes whilst the canopy was placed over their heads. The volume of oxygen consumed (*V*O2) and volume of carbon dioxide produced (*V*CO2) were calculated from the differences between inspired and expired air.

Participants then consumed a standard 75g glucose drink over 5 minutes and remained at rest for 120 minutes. Urine was collected during the test for measurement of urinary nitrogen excretion. Indirect calorimetry was repeated at 60 and 120 minutes after ingestion of glucose. Blood samples were collected through the intravenous cannula at 30‑minute intervals after ingestion of glucose for analysis of glucose, insulin and NEFA.

**Analytical Methods**

Glycated haemoglobin, plasma glucose, urinary nitrogen, serum lipids, insulin and C­peptide concentrations were measured by the Department of Clinical Biochemistry, Southampton General Hospital. Glucose, lipids and urinary nitrogen were measured using commercial enzymatic assays (Beckman Coulter Ltd, High Wycombe, UK). Insulin and C‑peptide were measured using commercial immunoassays (Siemens Healthcare Ltd, Camberley, UK). Glycated haemoglobin was measured using capillary electrophoresis (Sebia UK Ltd, Camberley, UK). Plasma NEFA and glycerol concentrations were measured by the NIHR Biomedical Research Unit (University of Southampton) using enzymatic methods on the Konelab 20 autoanalyser (Thermo Scientific, Abingdon, UK). LDL cholesterol was calculated using the Friedewald equation.[10](#_ENREF_10)

**Intervention**

Participants were randomly assigned to receive low dose (30 mg/day) rhIGF­I/rhIGFBP­3 complex, high dose (60 mg/day) rhIGF­I/rhIGFBP­3 complex or placebo. Insmed Incorporated (Virginia, USA) provided the rhIGF­I/rhIGFBP­3 complex (Mecasermin Rinfabate, iPLEXTM 60 mg/ml) and matched placebo. Drug vials were stored frozen at ­20°C until 30 minutes prior to injection when the required dose was allowed to thaw at room temperature. The injection technique was demonstrated to each volunteer prior to the first dose. Participants self­administered the drug subcutaneously with their evening meal for 28 consecutive days. All participants were reminded to inject the drug by daily text message and adherence was assessed by completion of a treatment diary and by collection of empty drug vials at the end of the treatment period. Participants were asked to continue their usual diet and physical activity during the drug administration period.

**Randomisation**

Insmed Incorporated prepared the rhIGF­I/rhIGFBP­3 and provided placebo in identical packaging, labelled with the allocation number. Insmed Incorporated generated the random allocation sequence in blocks of varying size for men and women, and University Hospital Southampton NHS Foundation Trust Pharmacy staff were responsible for dispensing the trial medication according to the allocation sequence. Participants and trial staff were blinded to interventions at all times.

On the day after the last injection (Day 28), participants returned to the WTCRF and all baseline assessments were repeated.

**Calculations and statistical analyses**

During indirect calorimetry, respiratory quotient was calculated as the ratio between *V*CO2 and *V*O2. Carbohydrate oxidation (CHOox) and lipid oxidation (Lipidox) rates were calculated from the following equations where Nu is urinary urea nitrogen excretion in grams per minute:[11](#_ENREF_11)

CHOox = (4.55\**V*CO2) – (3.21\**V*O2) – (2.87\*Nu)

Lipidox = (1.67\**V*O2) – (1.67\**V*CO2) – (1.92\*Nu)

Area under the curve (AUC) calculations for glucose, insulin and NEFA were performed using the trapezoidal method. The homeostatic model assessment (HOMA‑IR) was used to estimate insulin sensitivity from fasting glucose and insulin results.[12](#_ENREF_12)

The sample size calculations were based on the predicted responses in serum biomarkers to exogenous IGF­I administration in healthy athletes. Power calculations were not performed for lipid and carbohydrate metabolic variables, as there were no pilot data on which to perform the necessary calculations. Differences in baseline results between treatment groups were assessed using ANOVA. The General Linear Model approach was used to compare the changes in lipid and carbohydrate variables in the treatment groups (low dose and high dose rhIGF‑1/rhIGFBP‑3), with the placebo group. For each variable, interaction with sex was investigated in the model and the results are presented for both sexes separately and for women and men combined. *P*<0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, USA) and STATA version 16 (StatCorp LLC, College Station, USA).

**RESULTS**

Table 1 includes the baseline characteristics of the groups. The 30 male participants (mean age 22.4±2.7 yrs) comprised 29 white Europeans and 1 Asian. The 26 female participants (mean age 21.7±2.4 yrs) comprised 20 white Europeans, 2 Asians, 1 African and 3 mixed race. In women, there were significant differences between treatment groups at baseline in mean cholesterol and fasting glucose. In men, there were significant differences between treatment groups at baseline in mean HbA1c.

No participant discontinued the study because of adverse effects related to the study medication. Some participants in all treatment groups reported local erythema and pain at the site of subcutaneous injections; it is likely that this was a reaction to the solvent used to dissolve the drug and placebo. These symptoms were mild and resolved completely after stopping treatment. Three participants in the high dose rhIGF-1/rhIGFBP‑3 group reported increased appetite during treatment.

**Lipid metabolism**

The effects of rhIGF-1/rhIGFBP‑3 administration on lipid measurements and lipid oxidation rates are shown in Table 1 and Figure 1. When the change in these variables in the treatment groups was compared with the placebo group, there was no significant interaction with sex for: fasting triglycerides (low dose *P*=0.504, high dose *P*=0.215), NEFA (low dose *P*=0.928, high dose *P*=0.546), glycerol (low dose *P*=0.990, high dose *P*=0.324), total cholesterol to HDL ratio (low dose *P*=0.597, high dose *P*=0.631), NEFA AUC (low dose *P*=0.815, high dose *P*=0.255) and lipid oxidation rates (low dose *P*=0.444, high dose *P*=0.682). Data from women and men for these variables were therefore combined. Compared with the placebo group, a significant reduction in fasting triglycerides was observed in the high dose group (*P*=0.030) but not the low dose group (*P*=0.390). There were no significant changes in fasting NEFA (low dose *P*=0.935, high dose *P*=0.330), glycerol (low dose *P*=0.880, high dose *P*=0.611), total cholesterol to HDL ratio (low dose *P*=0.360, high dose *P*=0.641), NEFA AUC (low dose *P*=0.733, high dose *P*=0.745) or lipid oxidation rates (low dose *P*=0.534, high dose *P*=0.705).

There was a significant interaction with sex for changes in total cholesterol (low dose *P*=0.021, high dose *P*=0.042), HDL cholesterol (low dose *P*=0.114, high dose *P*=0.014) and LDL cholesterol (low dose *P*=0.045, high dose *P*=0.333). Data from women and men for these variables were therefore analysed separately. Compared with the placebo group, there was a significant increase in total cholesterol in women in the high dose group (*P*=0.003), but not the low dose group (*P*=0.066). There were no significant changes in total cholesterol in men in the low dose (*P*=0.149) or high dose (*P*=0.769) groups. There was also a significant increase in HDL cholesterol in women in the high dose group (*P*=0.001), but not the low dose group (*P*=0.090), and there were no significant changes in HDL cholesterol in men in the low dose (*P*=0.569) or high dose (*P*=0.833) groups. There was a significant increase in LDL cholesterol in women in the high dose group (*P*=0.008), but not the low dose group (*P*=0.088), and there were no significant changes in LDL cholesterol in men in the low dose (*P*=0.253) or high dose (*P*=0.160) groups.

**Carbohydrate metabolism**

The effects of rhIGF-1/rhIGFBP‑3 administration on carbohydrate metabolism and carbohydrate oxidation rates are shown in Table 1 and Figure 2. When the change in these variables in the treatment groups was compared with the placebo group, several variables revealed significant interactions with sex. Therefore, these carbohydrate metabolism data were analysed for both sexes combined and for women and men separately (Table 1). Compared with the placebo group, there was a significant reduction in fasting glucose in women in the low dose group (*P*=0.045), but not the high dose group (*P*=0.471). There were no significant changes in fasting glucose in men in the low dose (*P*=0.938) or high dose (*P*=0.128) groups. There were also significant reductions in fasting insulin and C‑peptide in women in both the low dose group (insulin:*P*=0.007; C-peptide:*P*=0.001) and the high dose group (insulin:*P*=0.010; C‑peptide:*P*=0.001). In men, there were no significant changes in either variable in the low dose group (insulin:*P*=0.469; C-peptide:*P*=0.250). In the high dose group, there was no significant change in insulin (*P*=0.119) but there was a significant reduction in C‑peptide (*P*=0.046). There was a significant reduction in HOMA‑IR in women in both the low dose group (*P*=0.006) and the high dose group (*P*=0.018), but no significant changes in men in either low dose (*P*=0.392) or high dose (*P*=0.094) groups. There were no significant changes in HbA1c in women in the low dose (*P*=0.597) or high dose (*P*=0.724) groups. Similarly, there were no significant changes in HbA1c in men (low dose group:*P*=0.666, high dose group:*P*=0.232). Finally, there were no significant changes in glucose AUC, insulin AUC or carbohydrate oxidation rates in any of the treatment groups in either women or men.

**DISCUSSION**

In this study we have shown the effects of rhIGF-1/rhIGFBP‑3 administration on lipid and glucose metabolism in young, healthy recreational athletes. Fasting triglycerides decreased after rhIGF-1/rhIGFBP‑3 administration. Total, HDL and LDL cholesterol increased in women after treatment with rhIGF-1/rhIGFBP­3, but not in men. These changes in serum lipid levels were associated with reduced insulin concentration and increased insulin sensitivity, again with larger effects apparent in women than men. rhIGF-1/rhIGFBP‑3 administration did not affect substrate utilisation measured by lipid and carbohydrate oxidation rates.

**Lipid metabolism**

There was a significant reduction in fasting triglycerides in response to rhIGF-1/rhIGFBP‑3 administration but there were no changes in glycerol or NEFA concentrations, thus suggesting a possible increase in triglyceride disposal or utilisation. Previous IGF-1 administration studies have demonstrated mixed effects on lipid profiles, depending on the population studied. The effects on serum lipoproteins of daily subcutaneous rhIGF-1 injections for seven days, were previously studied in ten healthy men.[13](#_ENREF_13) There was a reduction in total cholesterol, apolipoprotein B and serum triglycerides in this previous study, but in contrast with our current findings the authors did not observe a significant reduction in insulin concentrations.[13](#_ENREF_13) Five days’ continuous subcutaneous rhIGF-1 administration to seven healthy men reduced fasting triglyceride concentrations (similar to the current study), and increased HDL cholesterol (similar to the current female participant group), compared with a saline administration period.[2](#_ENREF_2) In this previous study, however, total cholesterol and LDL cholesterol were unchanged.[2](#_ENREF_2) The authors concluded that the effects of rhIGF-1 on lipid metabolism were linked to its effects on insulin secretion and insulin resistance, and this is discussed further below.

A decrease in triglycerides was also observed when rhIGF-1/rhIGFBP‑3 complex was administered to people with type 2 diabetes (mean age 56 years) for seven days.[14](#_ENREF_14) These authors found that total cholesterol decreased after rhIGF-1/rhIGFBP‑3 administration, whereas in our current study of healthy young adults, total, LDL and HDL cholesterol increased in women. When rhIGF-1/rhIGFBP‑3 was administered to people with type 1 diabetes (mean age 27 years) for two weeks, there was a significant reduction in total cholesterol but no change in triglyceride concentrations.[15](#_ENREF_15) In comparison with the current study population, the participants in those previous studies were older and had altered physiology in terms of reduced insulin secretion and/or reduced insulin sensitivity, and therefore it is difficult to compare the results between these populations. It is known that insulin can lower serum triglycerides through the stimulation of lipoprotein lipase (LPL).[16](#_ENREF_16) Insulin inhibits lipolysis and promotes fat storage within adipose tissue through the inhibition of hormone‑sensitive lipase and adipose triglyceride lipase.[17](#_ENREF_17) These inhibitory or ‘chalonic’ effects on lipolysis and ketogenesis are responsible for most of the physiological effect of insulin on lipid metabolism.[18](#_ENREF_18) It appears that rhIGF­I/rhIGFBP­3 administration has similar triglyceride‑lowering effects. The mechanism of this is unclear as previous studies have demonstrated differing effects between IGF­I and insulin on LPL activity in adipose tissue,[19](#_ENREF_19) and while IGF receptors are present on preadipocytes, mature adipocytes do not express functional IGF receptors.[1](#_ENREF_1)

When interpreting the effects of rhIGF­I administration on lipid profile, it is important to bear in mind the influence of growth hormone (GH) on lipid metabolism. In the current study population, we have reported previously that GH concentrations were suppressed by rhIGF‑1/rhIGFBP‑3 administration in both women and men, as expected.[9](#_ENREF_9) It is known that rhGH therapy in adults with GH deficiency has beneficial effects on lipid profile with decreased total and LDL cholesterol, decreased apolipoprotein B,[20](#_ENREF_20) and increased HDL cholesterol.[21](#_ENREF_21) Furthermore, when rhGH was administered as a continuous subcutaneous infusion to eight overweight men, there was a transient increase in VLDL but sustained decrease in LDL cholesterol.[22](#_ENREF_22) The authors concluded that changes in GH, IGF-1 and insulin concentrations were having mixed effects on lipoprotein metabolism.

The effects of rhIGF­I administration on lipid profile in GH deficiency have also been investigated; when rhIGF­I was administered for eight weeks to eight adults with GH deficiency, there were no significant changes in triglycerides, total cholesterol, HDL cholesterol or LDL cholesterol.[23](#_ENREF_23) When rhGH was administered to the same group for eight weeks, however, there was a significant decrease in LDL cholesterol and increase in triglycerides. This supported the concept that IGF-1 mediated only some of the metabolic actions of GH *in vivo*, though the mechanism of these divergent effects on lipid metabolism is uncertain.[23](#_ENREF_23) Olivecrona *et al.* investigated changes in serum lipoprotein concentrations in eleven men with idiopathic osteoporosis, who were treated for seven days with rhGH or rhIGF-1.[24](#_ENREF_24) They showed that rhGH administration caused a significant decrease in LDL cholesterol, while HDL cholesterol was unchanged and triglyceride concentrations increased. rhIGF-1 administration, however, had no significant effects on HDL cholesterol, LDL cholesterol or triglyceride concentrations in this population, again suggesting that IGF-1 and GH have differing effects on lipid metabolism and lipoprotein concentrations. These variable effects of rhIGF‑1 and rhIGF‑1/rhIGFBP‑3 administration on lipid profile components in women and men, in the current and previous studies, are also likely to reflect the interactions between the GH/IGF endocrine axis and oestrogen and other sex-specific hormones.

IGF­I also has variable effects on lipid oxidation, depending on the duration of treatment and the population studied. When rhIGF-1 was administered to eight healthy volunteers via a continuous subcutaneous infusion (10µg/kg.h for five days), an increase in lipid oxidation rates was observed.[25](#_ENREF_25) Similarly, rhIGF-1 administration increased lipid oxidation rates after seven days of treatment in adults with GH deficiency,[26](#_ENREF_26) but lipid oxidation rates were unchanged after eight weeks of rhIGF­I administration in a subsequent study in adults with GH deficiency.[23](#_ENREF_23) The difference between these studies was attributed to an acute reduction in insulin production in the earlier short‑term study, resulting in increased lipolysis and lipid oxidation. When rhIGF-1 was administered to a group of ten adults with GH insensitivity syndrome (GHIS) for eight weeks, increased lipolysis and increased lipid oxidation rates were observed.[27](#_ENREF_27) In the current study, no significant changes in lipid oxidation rates were observed using indirect calorimetry, after 28 days of rhIGF-1/rhIGFBP‑3 administration. It appears that prolonged IGF­I administration (at the doses given in this study) does not stimulate lipid oxidation in healthy volunteers with normal physiology, in contrast with its effects in participants with longstanding deficiencies in GH or IGF­I.

**Carbohydrate metabolism**

rhIGF-1/rhIGFBP‑3 administration increased insulin sensitivity in this study and insulin concentrations were suppressed as a result. The effects on carbohydrate metabolism included a reduction in fasting C‑peptide in both women and men, and a reduction in fasting glucose, insulin, C‑peptide and HOMA­IR in women only. As discussed above with regards to lipid metabolism, the effects on carbohydrate metabolism are a result of the interplay between the actions of IGF-1, GH and insulin, and suppression of GH secretion is likely the major contributor to increased insulin sensitivity. Simpson *et al.* investigated these effects in people with type 1 diabetes; after suppressing endogenous GH secretion with the somatostatin analogue octreotide, IGF­1 administration reduced hepatic glucose output and increased peripheral glucose uptake.[28](#_ENREF_28) This suggested that IGF­1 has a direct effect on glucose metabolism, independent of its role in suppressing GH secretion. Other studies have demonstrated a direct role of IGF­1 in increasing glucose transport into skeletal muscle and increasing muscle glycogen synthesis.[29-31](#_ENREF_29) The effects of rhIGF‑1/IGFBP‑3 administration in this study were more apparent in the fasting state (fasting glucose, insulin, C‑peptide, HOMA‑IR) than after glucose challenge (glucose and insulin AUC), again reflecting the role of IGF‑1 in suppressing GH secretion and of GH in antagonising the actions of insulin during postprandial carbohydrate metabolism.[1](#_ENREF_1),[32](#_ENREF_32) A further contributing factor to the glucose challenge response is the serum concentration of IGF binding proteins; insulin suppresses IGFBP‑1 secretion in normal physiology and thus increases free IGF‑1.[33](#_ENREF_33) These interactions between free IGF‑1, IGFBP‑1 and other IGF binding proteins during glucose challenge are likely to change after rhIGF‑1/rhIGFBP‑3 administration. Indeed, the Mecasermin rinfabate rhIGF‑1/IGFBP‑3 complex was developed as a therapeutic agent to provide a stable pool of circulating IGF‑1 with reduced incidence of side effects such as hypoglycaemia.[3](#_ENREF_3) It is likely that rhIGF‑1 alone, if administered to healthy athletes, would have greater effect on glucose and insulin responses during OGTT.

The insulin sensitivity results of the current study are in keeping with those of previous studies in which rhIGF‑1/rhIGFBP‑3 was administered to people with diabetes. Fifteen participants with type 1 diabetes were given rhIGF-1/rhIGFBP­3 complex for two days, which resulted in decreased overnight insulin requirements to maintain euglycaemia and improved insulin sensitivity.[34](#_ENREF_34) Seven days’ administration of rhIGF-1/rhIGFBP‑3 to 39 people with type 2 diabetes caused reductions in fasting glucose and mean daily glucose concentration.[14](#_ENREF_14) Administration of this complex has also been associated with improved glycaemic control in people with severe insulin resistance.[35](#_ENREF_35)

No significant changes in carbohydrate oxidation rates were observed in any of the treatment groups in this study. This agrees with the findings from previous studies in which rhIGF­1 was administered to eight healthy volunteers for five days,[25](#_ENREF_25) eight adults with GH deficiency for seven days[26](#_ENREF_26) and eight adults with GH deficiency for eight weeks.[23](#_ENREF_23) These carbohydrate oxidation results again reflect the combined effects of IGF­1 acting directly on carbohydrate oxidation, along with its suppression of GH and insulin secretion.

It is interesting to compare the results of this study with the metabolic abnormalities seen in acromegaly, a condition characterised by excess circulating levels of both GH and IGF‑1. Acromegaly is associated with dysregulated glucose metabolism and increased risk of cardiovascular disease.[36](#_ENREF_36) Common lipid profile alterations in acromegaly include hypertriglyceridaemia and low HDL cholesterol,[37](#_ENREF_37) while impaired glucose tolerance and diabetes mellitus are present in 30% to 50% of patients with acromegaly at the time of diagnosis.[38](#_ENREF_38),[39](#_ENREF_39) This contrasts with the current findings where rhIGF‑1/rhIGFBP‑3 administration was associated with reduced triglycerides, increased HDL and improved insulin sensitivity. We have previously described the changes in circulating IGF‑1 and GH concentrations in this rhIGF‑1/rhIGFBP‑3 administration study: there was an approximate 3.5- to 4.5-fold increase in serum IGF‑1 concentrations in the rhIGF‑1/rhIGFBP‑3 groups during treatment (Table 1), and this was associated with suppressed serum GH concentrations, as expected.[9](#_ENREF_9) This highlights again the interplay between GH and IGF‑1 in lipid and carbohydrate homeostasis because the supra-physiological IGF‑1 concentrations observed in this study (similar to acromegaly) are now acting to reduce GH secretion and overall to enhance insulin sensitivity.

In conclusion, the administration of rhIGF-1/rhIGFBP‑3 to recreational athletes caused a reduction in insulin concentration, increased insulin sensitivity and had significant effects on lipid profile including a decrease in fasting triglycerides. These changes are in keeping with GH suppression, as well as possible direct effects of IGF­1, and emphasise the important role of the GH‑IGF axis in glucose and lipid homeostasis.

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**Table 1.** **Markers of lipid and carbohydrate metabolism before and after 28 days of treatment in 26 female and 30 male recreational athletes. NEFA = Non­Esterified Fatty Acids. \*Significant difference (*P* < 0.05) compared with the change in the placebo group (see Results text). Serum IGF‑I concentrations at the equivalent timepoints are illustrated for each treatment group,**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **WOMEN AND MEN COMBINED** | **Treatment groups** | | | | | | | | |
| **Placebo (n=18)** | | | **Low dose IGF-1 (n=19)** | | | **High dose IGF-1 (n=19)** | | |
| **Day 0** | **Day 28** | **Mean change from Day 0**  **(95% CI)** | **Day 0** | **Day 28** | **Mean change from Day 0**  **(95% CI)** | **Day 0** | **Day 28** | **Mean change from Day 0**  **(95% CI)** |
| **Mean IGF‑1 (SD), mcg/L** | 287 (52) | 275 (45) | -12 (-33 to 3) | 260 (73) | 954 (257) | 694 (585 to 803) | 261 (71) | 1011 (341) | 750 (590 to 911) |
| **Mean fasting triglycerides (SD), mmol/L** | 1.1 (0.4) | 1.1 (0.7) | 0 (-0.3 to 0.3) | 0.9 (0.3) | 0.8 (0.3) | -0.1 (-0.2 to 0) | 0.9 (0.4) | 0.6 (0.2)\* | -0.3 (-0.4 to -0.1) |
| **Mean fasting NEFA (SD), micromol/L** | 415 (149) | 389 (190) | -26 (-156 to 105) | 461 (212) | 443 (169) | -18 (-142 to 106) | 455 (138) | 522 (248) | 67 (-95 to 229) |
| **Mean fasting glycerol (SD), micromol/L** | 55.0 (28.3) | 52.3 (32.9) | -2.7 (-23.0 to 17.4) | 55.3 (34.4) | 54.3 (27.1) | -1.0 (-15.1 to 13.1) | 55.2 (33.5) | 58.3 (29.3) | 3.1 (-14.0 to 20.2) |
| **Mean fasting total cholesterol (SD), mmol/L** | 4.2 (0.6) | 4.2 (0.6) | 0 (-0.2 to 0.2) | 4.6 (1.0) | 4.6 (0.9) | 0 (-0.3 to 0.3) | 3.9 (0.6) | 4.3 (0.6) | 0.4 (0.1 to 0.7) |
| **Mean fasting HDL cholesterol (SD), mmol/L** | 1.3 (0.3) | 1.3 (0.4) | 0 (-0.1 to 0.1) | 1.4 (0.4) | 1.4 (0.3) | 0 (-0.1 to 0.1) | 1.3 (0.2) | 1.4 (0.3) | 0.1 (0 to 0.2) |
| **Mean fasting total cholesterol:HDL ratio (SD)** | 3.4 (1.0) | 3.6 (1.1) | 0.2 (-0.1 to 0.4) | 3.4 (0.9) | 3.4 (1.0) | 0 (-0.2 to 0.2) | 3.1 (0.7) | 3.1 (0.7) | 0 (-0.1 to 0.2) |
| **Mean fasting LDL cholesterol (SD), mmol/L** | 2.4 (0.5) | 2.4 (0.5) | 0 (-0.1 to 0.2) | 2.8 (0.9) | 2.8 (0.9) | 0 (-0.2 to 0.3) | 2.2 (0.6) | 2.6 (0.6) | 0.4 (0.2 to 0.6) |
| **Mean NEFA AUC (SD), micromol/L x min** | 15418 (5040) | 15668 (4643) | 250 (-3121 to 3620) | 16167 (5669) | 17280 (6199) | 1113 (-2075 to 4301) | 16549 (6026) | 16020 (6038) | -529 (-4821 to 3763) |
| **Mean fasting lipid oxidation rate (SD), mg/min** | 42.9 (16.6) | 35.9 (22.7) | -7.0 (-18.0 to 4.0) | 40.0 (21.3) | 39.9 (37.0) | -0.1 (-21.3 to 20.9) | 38.0 (19.8) | 34.9 (21.1) | -3.1 (-21.8 to 15.7) |
| **Mean fasting glucose (SD), mmol/L** | 4.6 (0.4) | 4.6 (0.4) | 0 (-0.2 to 0.1) | 4.8 (0.4) | 4.6 (0.3) | -0.2 (-0.4 to 0) | 4.6 (0.3) | 4.4 (0.3) | -0.2 (-0.4 to 0) |
| **Mean fasting insulin (SD), mU/L** | 4.8 (2.0) | 4.8 (2.9) | 0 (-1.2 to 1.1) | 4.6 (2.4) | 2.6 (1.7) | -2.0 (-3.2 to -0.9) | 4.9 (2.5) | 2.3 (1.0) | -2.6 (-3.7 to -1.3) |
| **Mean fasting C­peptide (SD), pmol/L** | 457 (145) | 442 (138) | -15 (-90 to 59) | 382 (127) | 223 (75) | -159 (-213 to 105) | 401 (122) | 208 (102) | -193 (-251 to 134) |
| **Mean HOMA­IR (SD), (mU\*mmol)/L2** | 1.0 (0.5) | 1.0 (0.7) | 0 (-0.3 to 0.2) | 1.0 (0.6) | 0.5 (0.4) | -0.5 (-0.7 to -0.2) | 1.0 (0.5) | 0.5 (0.2) | -0.5 (-0.8 to -0.3) |
| **Mean HbA1c (SD), %** | 5.3 (0.3) | 5.2 (0.3) | -0.1 (-0.3 to 0.1) | 5.3 (0.3) | 5.1 (0.3) | -0.2 (-0.3 to 0) | 5.2 (0.3) | 5.1 (0.3) | -0.1 (-0.2 to 0) |
| **Mean HbA1c (SD), mmol/mol** | 34 (3.3) | 33 (3.3) | -1 (-3.3 to 1.1) | 34 (3.3) | 32 (3.3) | -2 (-3.3 to 0) | 33 (3.3) | 32 (3.3) | -1 (-2 to 0) |
| **Mean glucose AUC (SD), mmol/L x min** | 608 (232) | 615 (142) | 7 (-86 to 101) | 654 (145) | 645 (159) | -9 (-69 to 52) | 636 (247) | 601 (213) | -35 (-131 to 60) |
| **Mean insulin AUC (SD), mU/L x min** | 3312 (2263) | 3105 (1812) | -207 (-1087 to 673) | 2100 (979) | 1898 (678) | -202 (-702 to 297) | 2643 (1377) | 1767 (886) | -876 (-1450 to –302) |
| **Mean fasting carbohydrate oxidation rate (SD), mg/min** | 156.4 (56.9) | 177.4 (75.4) | 21.0 (-4.2 to 46.2) | 162.4 (52.8) | 135.8 (77.0) | -26.6 (-89.9 to 36.5) | 155.2 (52.8) | 162.0 (66.7) | 6.8 (-46.3 to 60.0) |
| **WOMEN** | **Female treatment groups** | | | | | | | | |
| **Placebo (n=8)** | | | **Low dose IGF-1 (n=9)** | | | **High dose IGF-1 (n=9)** | | |
| **Day 0** | **Day 28** | **Mean change from Day 0**  **(95% CI)** | **Day 0** | **Day 28** | **Mean change from Day 0**  **(95% CI)** | **Day 0** | **Day 28** | **Mean change from Day 0**  **(95% CI)** |
| **Mean IGF‑1 (SD), mcg/L** | 285 (61) | 270 (68) | -15 (-66 to 35) | 284 (94) | 1116 (214) | 832 (681 to 984) | 279 (87) | 1125 (418) | 846 (524 to 1166) |
| **Mean fasting triglycerides (SD), mmol/L** | 0.9 (0.3) | 0.8 (0.3) | -0.1 (-0.4 to 0.2) | 0.9 (0.4) | 0.8 (0.4) | -0.1 (-0.3 to 0.2) | 0.8 (0.2) | 0.6 (0.2) | -0.2 (-0.3 to -0.1) |
| **Mean fasting NEFA (SD), micromol/L** | 516 (134) | 441 (111) | -75 (-293 to 143) | 490 (202) | 415 (173) | -75 (-244 to 94) | 422 (110) | 380 (75) | -42 (-149 to 66) |
| **Mean fasting glycerol (SD), micromol/L** | 78.8 (29.7) | 69.5 (35.6) | -9.4 (-62.5 to 43.8) | 71.4 (38.5) | 64.3 (30.8) | -7.0 (-27.8 to 13.8) | 72.4 (40.7) | 57.0 (35.0) | -15.4 (-36.2 to 5.4) |
| **Mean fasting total cholesterol (SD), mmol/L** | 4.1 (0.6) | 3.9 (0.5) | -0.1 (-0.4 to 0.2) | 4.6 (0.5) | 4.9 (0.8) | 0.3 (-0.1 to 0.7) | 3.8 (0.4) | 4.4 (0.5)\* | 0.6 (0.3 to 1.0) |
| **Mean fasting HDL cholesterol (SD), mmol/L** | 1.6 (0.2) | 1.5 (0.4) | -0.1 (-0.2 to 0.1) | 1.5 (0.4) | 1.5 (0.4) | 0 (0 to 0.2) | 1.4 (0.3) | 1.6 (0.2)\* | 0.2 (0.1 to 0.3) |
| **Mean fasting total cholesterol:HDL ratio (SD)** | 2.6 (0.4) | 2.8 (0.7) | 0.1 (-0.3 to 0.6) | 3.4 (1.1) | 3.5 (1.3) | 0.1 (-0.2 to 0.4) | 2.8 (0.4) | 2.8 (0.5) | 0 (-0.2 to 0.1) |
| **Mean fasting LDL cholesterol (SD), mmol/L** | 2.1 (0.5) | 2.1 (0.4) | 0 (-0.2 to 0.2) | 2.8 (0.8) | 3.1 (1.1) | 0.3 (-0.1 to 0.6) | 2.0 (0.3) | 2.5 (0.6)\* | 0.5 (0.2 to 0.8) |
| **Mean NEFA AUC (SD), micromol/L x min** | 15,086 (5447) | 14,624 (3040) | -462 (-6655 to 5731) | 17,229 (8535) | 16,622 (8450) | -608 (-2433 to 1218) | 17,051 (8125) | 12,748 (3919) | -4303 (-11256 to 2650) |
| **Mean fasting lipid oxidation rate (SD), mg/min** | 44.7 (19.3) | 40.5 (23.5) | -4.2 (-20.1 to 12.0) | 28.0 (16.4) | 21.9 (18.1) | -6.1 (-22.7 to 10.5) | 28.2 (13.9) | 31.2 (15.9) | 3.0 (-15.5 to 21.5) |
| **Mean fasting glucose (SD), mmol/L** | 4.4 (0.3) | 4.4 (0.3) | 0 (-0.3 to 0.4) | 4.9 (0.4) | 4.5 (0.3)\* | -0.4 (-0.7 to -0.1) | 4.5 (0.2) | 4.4 (0.2) | -0.1 (-0.4 to 0.2) |
| **Mean fasting insulin (SD), mU/L** | 4.1 (1.4) | 4.4 (0.8) | 0.4 (-0.9 to 1.7) | 5.4 (2.7) | 2.5 (1.8)\* | -2.9 (-4.5 to -1.4) | 5.2 (2.9) | 2.4 (0.9)\* | -2.8 (-5.1 to -0.4) |
| **Mean fasting C­peptide (SD), pmol/L** | 412 (96) | 461 (32) | 49 (-32 to 130) | 418 (162) | 223 (78)\* | -195 (-299 to -90) | 461 (135) | 249 (123)\* | -212 (-338 to -85) |
| **Mean HOMA­IR (SD), (mU\*mmol)/L2** | 0.8 (0.3) | 0.9 (0.2) | 0.1 (-0.2 to 0.4) | 1.2 (0.7) | 0.5 (0.4)\* | -0.7 (-1.1 to -0.3) | 1.0 (0.5) | 0.5 (0.2)\* | -0.6 (-1.1. to -0.1) |
| **Mean HbA1c (SD), %** | 5.3 (0.3) | 5.1 (0.2) | -0.2 (-0.4 to 0) | 5.4 (0.2) | 5.1 (0.3) | -0.3 (-0.5 to -0.1) | 5.4 (0.1) | 5.1 (0.2) | -0.2 (-0.4 to -0.1) |
| **Mean HbA1c (SD), mmol/mol** | 34 (3.3) | 32 (2.2) | -2 (-5 to 0) | 36 (2.2) | 32 (3.3) | -4 (-6 to -1) | 36 (1.1) | 32 (2.2) | -4 (-4 to -1) |
| **Mean glucose AUC (SD), mmol/L x min** | 494 (287) | 551 (166) | 58 (-130 to 245) | 585 (217) | 567 (261) | -18 (-125 to 90) | 484 (245) | 464 (147) | 20 (-218 to 178) |
| **Mean insulin AUC (SD), mU/L x min** | 3035 (2557) | 3160 (975) | 125 (-1634 to 1884) | 2211 (1000) | 1785 (727) | -426 (-1830 to 978) | 2027 (991) | 1428 (519) | -599 (-1591 to 393) |
| **Mean fasting carbohydrate oxidation rate (SD), mg/min** | 117.5 (24.8) | 128.0 (37.3) | 10.6 (-24.7 to 45.8) | 162.1 (28.7) | 153.3 (48.4) | -8.7 (-68.5 to 51.1) | 173.9 (28.2) | 148.0 (41.9) | -25.9 (-72.2 to 20.5) |
| **MEN** | **Male treatment groups** | | | | | | | | |
| **Placebo (n=10)** | | | **Low dose IGF-1 (n=10)** | | | **High dose IGF-1 (n=10)** | | |
| **Day 0** | **Day 28** | **Mean change from Day 0**  **(95% CI)** | **Day 0** | **Day 28** | **Mean change from Day 0**  **(95% CI)** | **Day 0** | **Day 28** | **Mean change from Day 0**  **(95% CI)** |
| **Mean IGF‑1 (SD), mcg/L** | 290 (59) | 277 (53) | -13 (-40 to 14) | 238 (42) | 807 (203) | 569 (441 to 697) | 245 (53) | 910 (230) | 665 (505 to 824) |
| **Mean fasting triglycerides (SD), mmol/L** | 1.2 (0.4) | 1.3 (0.8) | 0.1 (-0.4 to 0.6) | 0.9 (0.3) | 0.8 (0.3) | -0.1 (-0.3 to 0.1) | 1.0 (0.5) | 0.6 (0.2) | -0.4 (-0.7 to -0.1) |
| **Mean fasting NEFA (SD), micromol/L** | 354 (125) | 358 (224) | 4 (-190 to 197) | 441 (226) | 463 (173) | 22 (-176 to 219) | 482 (158) | 636 (282) | 154 (-139 to 447) |
| **Mean fasting glycerol (SD), micromol/L** | 40.8 (15.6) | 41.9 (28.0) | 1.2 (-20.6 to 22.9) | 44.1 (27.9) | 47.3 (23.3) | 3.2 (-19.0 to 25.4) | 41.4 (19.0) | 59.4 (25.9) | 17.9 (-6.8 to 42.7) |
| **Mean fasting total cholesterol (SD), mmol/L** | 4.3 (0.6) | 4.4 (0.6) | 0.1 (-0.2 to 0.4) | 4.6 (1.3) | 4.3 (0.9) | -0.3 (-0.7 to 0.2) | 4.1 (0.7) | 4.3 (0.6) | 0.2 (-0.2 to 0.6) |
| **Mean fasting HDL cholesterol (SD), mmol/L** | 1.1 (0.3) | 1.1 (0.2) | 0 (-0.1 to 0.1) | 1.4 (0.4) | 1.3 (0.3) | -0.1 (-0.2 to 0.1) | 1.3 (0.2) | 1.3 (0.2) | 0 (-0.1 to 0.2) |
| **Mean fasting total cholesterol:HDL ratio (SD)** | 4.1 (0.9) | 4.2 (0.9) | 0.1 (-0.3 to 0.5) | 3.4 (0.7) | 3.3 (0.6) | -0.1 (-0.3 to 0.2) | 3.3 (0.8) | 3.4 (0.8) | 0.1 (-0.1 to 0.4) |
| **Mean fasting LDL cholesterol (SD), mmol/L** | 2.7 (0.4) | 2.7 (0.4) | 0.1 (-0.2 to 0.3) | 2.8 (1.1) | 2.6 (0.8) | -0.1 (-0.5 to 0.2) | 2.4 (0.7) | 2.7 (0.6) | 0.3 (0.1 to 0.6) |
| **Mean NEFA AUC (SD), micromol/L x min** | 15,677 (5021) | 16,480 (5638) | 803 (-4094 to 5700) | 15,695 (4481) | 17,572 (5528) | 1878 (-2929 to 6685) | 16,159 (4263) | 18,565 (6339) | 2406 (-3403 to 8215) |
| **Mean fasting lipid oxidation rate (SD), mg/min** | 41.4 (14.9) | 31.9 (22.6) | -9.5 (-27.8 to 8.9) | 52.1 (19.5) | 57.9 (43.7) | 5.8 (-42.2 to 53.7) | 51.0 (19.9) | 39.9 (27.5) | -11.1 (-57.2 to 35.0) |
| **Mean fasting glucose (SD), mmol/L** | 4.8 (0.4) | 4.8 (0.4) | -0.1 (-0.3 to 0.1) | 4.7 (0.4) | 4.7 (0.2) | -0.1 (-0.3 to 0.1) | 4.7 (0.3) | 4.5 (0.3) | -0.3 (-0.5 to -0.1) |
| **Mean fasting insulin (SD), mU/L** | 5.5 (2.3) | 5.0 (3.8) | 0.5 (-2.4 to 1.5) | 4.0 (2.0) | 2.7 (1.8) | -1.3 (-3.2 to 0.7) | 4.5 (2.0) | 2.3 (1.2) | -2.3 (-3.6 to -1.0) |
| **Mean fasting C­peptide (SD), pmol/L** | 494 (170) | 427 (186) | -67 (-189 to 55) | 349 (81) | 222 (76) | -128 (-186 to -69) | 347 (82) | 172 (65)\* | -175 (-222 to -128) |
| **Mean HOMA­IR (SD), (mU\*mmol)/L2** | 1.2 (0.5) | 1.1 (0.9) | -0.1 (-0.5 to 0.4) | 0.8 (0.4) | 0.6 (0.4) | -0.3 (-0.7 to 0.1) | 1.0 (0.4) | 0.5 (0.3) | -0.5 (-1.2 to -0.5) |
| **Mean HbA1c (SD), %** | 5.4 (0.2) | 5.3 (0.2) | -0.1 (-0.3 to 0) | 5.2 (0.2) | 5.1 (0.3) | -0.1 (-0.3 to 0.1) | 5.1 (0.3) | 5.1 (0.4) | 0 (-0.2 to 0.2) |
| **Mean HbA1c (SD), mmol/mol** | 36 (2.2) | 34 (2.2) | -2 (4 to 0) | 33 (2.2) | 32 (3.3) | -1 (4 to 1) | 32 (3.3) | 32 (4.4) | 0 (-2 to 2) |
| **Mean glucose AUC (SD), mmol/L x min** | 709 (102) | 672 (93) | -37 (-140 to 65) | 684 (102) | 680 (90) | -5 (-94 to 84) | 771 (162) | 722 (190) | -50 (-155 to 57) |
| **Mean insulin AUC (SD), mU/L x min** | 3558 (2091) | 3056 (2393) | -502 (-1526 to 523) | 2045 (1033) | 1955 (696) | -90 (-735 to 554) | 3259 (1488) | 2106 (1073) | -1153 (-1948 to -359) |
| **Mean fasting carbohydrate oxidation rate (SD), mg/min** | 191.0 (55.4) | 221.3 (74.5) | 30.3 (-12.0 to 72.6) | 162.8 (72.8) | 118.2 (99.8) | -44.7 (-184.6 to 95.2) | 130.3 (69.5) | 180.7 (91.5) | 50.4 (-72.6 to 173.4) |

**FIGURE LEGENDS**

**Figure 1.** The effects of rhIGF-1/rhIGFBP‑3 administration on lipid profile in recreational athletes (women: black lines; men: blue, dashed lines). Fasting triglycerides (A), non-esterified fatty acids (NEFA, B), glycerol (C), total cholesterol (D), LDL cholesterol (E) and HDL cholesterol (F) were measured at baseline and after 28 days’ subcutaneous administration of rhIGF-1/rhIGFBP‑3. \*Significant difference (*P* < 0.05) compared with change in the placebo group (see Results text).

**Figure 2.** The effects of rhIGF-1/rhIGFBP‑3 administration on carbohydrate metabolism in recreational athletes (women: black lines; men: blue, dashed lines). Fasting glucose (A), insulin (B), C‑peptide (C), HOMA‑IR (D) and HbA1c (E) were measured at baseline and after 28 days’ subcutaneous administration of rhIGF-1/rhIGFBP‑3. \*Significant difference (*P* < 0.05) compared with change in the placebo group (see Results text).