

Systemic Effects of Growth Hormone in Growth Hormone Deficient Adults: A Meta-Analysis of 48 Prospective Studies

Alexander W. Pastuszak*, Win Shun Lai*, Mohit Khera, Larry I. Lipshultz#

Scott Department of Urology, Baylor College of Medicine, Houston, USA

Email: #larryl@bcm.edu

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ABSTRACT

Introduction: The use of growth hormone (GH) treatment in GH deficiency (GHD) continues to increase. However, individual controlled trials of the efficacy and safety of GH have involved relatively few patients and yielded variable results. We seek to analyze the overall effect of GH treatment on various parameters by performing a contemporary meta-analysis of the efficacy and safety of GH administration. **Methods:** Meta-analysis of 48 blinded, placebo controlled, randomized clinical studies of GH treatment in GHD adults published up to June 2011 was performed. Analyzed variables included anthropomorphic measurements (waist-hip ratio (WHR), lean body mass (LBM)/fat free mass (FFM), trunk fat (TrF), total body water (TBW), fat mass (FM), and body mass index (BMI)); cardiovascular (CV) parameters (systolic/diastolic blood pressure (SBP, DBP), heart rate (HR), stroke volume (SV), LDL, HDL, total cholesterol (TChol), triglycerides (TG), apolipoprotein B (ApoB), C-reactive protein (CRP)); and diabetes parameters (fasting insulin and glucose, hemoglobin A1c (HgbA1c)). Effect sizes (ES) were used to determine significance and weighted mean differences between GH and control were used to quantify size of effect. **Results:** 2231 adults with growth hormone deficiency were included. Significant beneficial changes resulting from GH administration were observed in the following variables: anthropomorphic—WHR, FM, LBM, FFM, TBW; cardiovascular—LDL, HDL, TChol, ApoB, CRP; significant adverse changes were seen in diabetic parameters—fasting insulin, fasting glucose, and HgbA1c. Compared to prior meta-analyses, larger ESs were observed for LDL, HDL, total cholesterol, fasting insulin and fasting glucose levels. **Conclusions:** GH administration in GHD adults results in improvement in anthropomorphic parameters, as well as CV parameters, but with worsening of diabetes markers. Data on long-term safety, including on CV effects and malignancy, as well as data assessing the role of GH replacement in combination with testosterone replacement continue to be sparse.

Keywords: Growth Hormone; Growth Hormone Deficiency; Meta-Analysis; Sex Steroids

1. Introduction

The use of growth hormone (GH) for the treatment of growth hormone deficiency (GHD), a form of hypopituitarism, continues to increase. However, most studies assessing the efficacy and safety of GH involve relatively few patients. Growth hormone deficiency in adults is associated with an increased mortality rate [1,2]. Previous studies have shown that GHD affects numerous health parameters including anthropomorphic and cardiovascular (CV) parameters, glucose and insulin sensitivity, and overall quality of life [3]. In addition, GH use by individuals without GHD continues, though no controlled studies are available to assess the effects in this setting, despite reports of deleterious effects of GH and/or anabolic steroids in these individuals [4-7].

Clinical trials have shown that GH therapy improves body fat parameters in the GHD population through an increase in lean body mass and a decrease in serum lipids, with variable effect sizes on these parameters observed between studies [8]. While this variability may be attributable to differences in the degree of GH deficiency, GH dose, therapy duration, sample size and/or composition, further evaluation in the form of additional controlled studies or meta-analyses is needed to clarify these points. Meta-analyses evaluating the effects of GH therapy are available, although numerous additional controlled studies have been published since the last significant report [9-12]. Moreover, recent studies have begun exploring the synergistic role of GH therapy in combination with androgen therapy in the healthy elderly population, which is likely to have future impact on the care of this population [13,14]. Thus, in light of the growing use of GH therapy and the addition of numerous controlled

*These authors contributed equally to the preparation of this manuscript.

#Corresponding author.

studies to the peer-reviewed literature, we performed a comprehensive, contemporary meta-analysis of the efficacy and safety of GH administration in GHD adults through a systematic review of blinded, randomized, placebo-controlled studies assessing GH efficacy and safety.

2. Materials and Methods

2.1. Data Sources and Searches

We searched the Medline (Ovid), Biosis, and EMBASE electronic databases from their years of inception to June 2011 for reports containing the following keywords: *growth hormone (GH), therapy, treatment, and growth hormone deficiency*. The search strategy was limited by study design to include only adults (19+ years old) in randomized, placebo-controlled clinical trials.

2.2. Study Selection

Inclusion of candidate studies by two of the authors (AWP, WSL) was based on the ability of the abstract and then the actual study to meet the inclusion criteria. We identified 45 randomized, blinded, placebo-controlled trials (RBPCTs) involving patients 19 years or older with GHD corresponding to GH levels $< 5 \mu\text{g/L}$ after stimulation testing using insulin and/or arginine [13-64], as recommended by the consensus guidelines for the diagnosis and treatment of adults with GHD [15] and also included 3 crossover studies that had been utilized in a prior meta-analysis for comparison [9,18,51,60] (**Figure 1**).

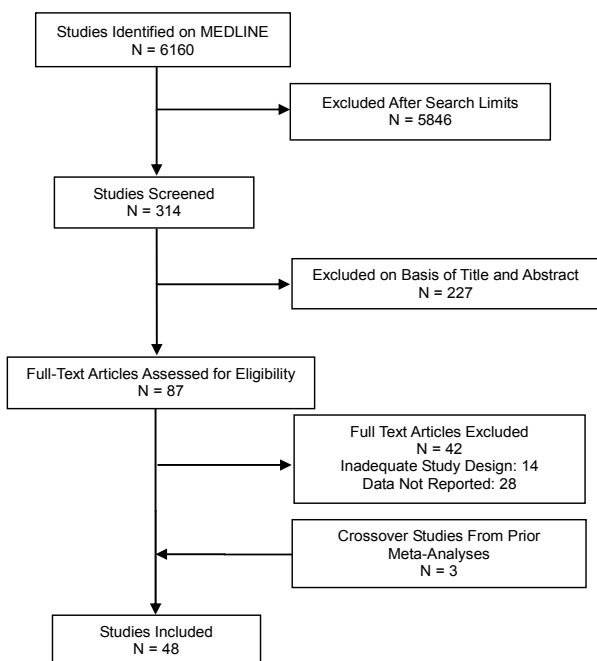


Figure 1. Identification of studies for inclusion in meta-analysis.

We also identified 2 RBPCTs assessing the effects of testosterone (T) and GH in order to compare these variables directly [13,14]. This study targeted variables which represent the effects of GH on anthropomorphic and CV parameters and have been frequently reported in prior studies examining the effects of GH: insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP3), waist-to-hip ratio (WHR), lean body mass (LBM), fat free mass (FFM), trunk fat (TrF), total body water (TBW), fat mass (FM), body mass index (BMI), diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR), stroke volume (SV), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TChol), apolipoprotein B (ApoB), C-reactive protein (CRP), E (Early (diastolic))/A (late, (Atrial) filling) ratio (EAR), fractional shortening (FS), left ventricular mass (LVM), fasting glucose, fasting insulin, and hemoglobin A1c (HgbA1c).

2.3. Data Extraction and Quality Assessment

Summary data reflecting net effects on each variable studied from each report were extracted by a single author (WSL) into a standard form and included number of subjects, subject age, sex, cause of GHD, GHD diagnostic modality, GH dose, duration of GH therapy, GH dosing frequency, adverse effects, study design, randomization method, blinding, and statistical methods, outcome measures, subjects lost to follow-up, and baseline and follow-up means and standard deviations (SD) for each variable.

2.4. Data Synthesis and Analysis

For primary analyses of outcome measures, we calculated standardized effect sizes (ES) using Hedges' g via a random-effects model for each trial, since such a model incorporates statistical heterogeneity and provides a more conservative estimate of pooled effect size than a fixed-effects model [65]. The ES was calculated as the mean difference (GH minus placebo) in the changes (follow-up minus baseline) for each outcome measure divided by the estimated variance of changes in the two groups, and weighted by the reciprocal of the variance. The variance-weighted mean difference (WMD) was calculated for each variable in order to determine absolute effects of GH administration on variables in the units of each variable. Heterogeneity between studies was assessed using a Q parameter as defined by Cochran [66]. Given that ES may be skewed due to the results of a single study, we performed sensitivity analysis by excluding the study with the largest sample population per outcome measured.

To determine the effects of GH dose, subject gender, GH treatment duration, and subject age, studies were

grouped based on the following and meta-analysis within each group performed: *GH dose*—studies utilizing <0.35 U/kg/week (low dose) and ≥ 0.35 U/kg/week of GH (high dose); *subject gender*—studies involving <50% female or $\geq 50\%$ female; *GH treatment duration*—studies with GH treatment for <6 months, or ≥ 6 months; *subject age*—studies involving patients <40 years old or ≥ 40 years old. To compare the effects of GH and T administration, meta-analysis of the 2 included studies was performed. All analyses were conducted using the Statistical Package for Social Sciences (SPSS) (SPSS Inc., Chicago, IL) for Windows and Apple Macintosh, and Microsoft Excel (Microsoft, Inc., Redmond, WA).

3. Results

A meta-analysis of 48 studies involving 2231 patients with GHD was performed to assess the effects of GH on anthropomorphic, CV, and carbohydrate metabolism parameters (**Table 1**). Results are presented in terms of effect size (ES) calculated using a random-effects model after a Q parameter calculation demonstrated minimal heterogeneity across studies, as well as in terms of the weighted mean difference (WMD) for each variable. Ninety-nine patients were lost or withdrew across all studies (**Table 1**). Causes of GHD were: 73% pituitary tumor, 11% idiopathic causes, and 16% other causes.

Table 1. Characteristics of studies included in the meta-analysis.

First Author	Year	Reference Number	Duration (Months)	% Female	Age (SD) (Years)	Total Subjects	Variables Evaluated	Subjects Lost
Cuneo, R.C.	1991	17	6	33	38.5 (ND)	24	FS, LVM, SV	
Cuneo, R.C.	1993	19	6	33	38.0 (9.8)	24	ApoB, HDL, LDL, Tchol, TG	
Beshyah, S.A.	1994	21	6	53	43.0 (ND)	36	DBP, EAR, EF, LVM, SBP	
Russell-Jones, D.L.	1994	22	2	56	46.6 (9.1)	18	ApoB, HDL, LDL, Tchol, TG	
Valcavi, R.	1995	25	12	30	47.2 (2.6)	20	EAR, EF, FS, HR, IGF1, LVM, SV	
Nass, R.	1995	24	6	25	44.7 (ND)	20	FS, IGF1, LBM, LVM	
Beshyah, S.A.	1995	23	6	53	44.0 (ND)	40	ApoB, Fasting Glucose, Fasting Insulin, HDL, LDL, Tchol, TG	
Böger, R.H.	1996	24	12	53	41.5 (2.8)	30	HDL, LDL, Tchol, TG	0
Webster, J.M.	1997	31	6	33	44.3 (10.0)	18	BMI, Fasting Glucose, Fasting Insulin, HgbA1c, Tchol	0
Nolte, W.	1997	30	12	47	41.6 (10.7)	32	HDL, IGF1, LDL, Tchol, TG	6
Hwu, C.M.	1997	29	6	63	29.5 (7.4)	16	BMI, Fasting Glucose, FM, HDL, IGF1, LDL, Tchol, TG, WHR	5
Christ, E.R.	1997	28	3	54	51.9 (16.2)	13	FM, IGF1SDS, IGFBP3SDS, LBM, TBW	0
Chipman, J.J.	1997	27	6	33	37.4 (ND)	165	Fasting Glucose, Fasting Insulin, HgbA1C	0
Cuneo, R.C.	1998	32	6	44	40.5 (1.5)	163	DBP, Fasting Glucose, FFM, HDL, IGF1SDS, IGFBP3, IGFBP3SDS, LDL, SBP, TBW, Tchol, TG	3
Leese, G.P.	1998	33	6	67	35.0 (12.1)	30	HDL, LDL, Tchol, TG	2
Russell-Jones, D.L.	1998	34	2	67	46.8 (2.6)	12	BMI, Fasting Glucose, Fasting Insulin, IGF1, LBM	0
Vahl, N.	1998	35	12	37	44.5 (1.8)	27	HDL, LDL, Tchol, TG	0
Bell, W.	1999	36	6	47	44.1 (7.4)	43	FFM, TBW	8
Christ, E.R.	1999	38	3	61	48.9 (5.3)	18	HDL, LDL, Tchol, TG	3
Rosenfalck, A.M.	1999	39	4	25	38.0 (10.6)	24	Fasting Glucose, Fasting Insulin, FM, LBM, TRF	0
Sönksen, P.H.	1999	48	3	57	49.5 (5.7)	14	Fasting Insulin, HDL, HgbA1c, IGF1SDS, IGFBP3SDS, LDL, Tchol, TG	0
Fernholm, R.	2000	40	6	19	68.5 (ND)	31	Fasting Insulin, FM, IGFBP3, LBM	0

Continued

Sesmiło, G.	2000	41	18	0	49.2 (9.7)	40	CRP, Fasting Glucose, Fasting Insulin, LDL, Tchol, TG	0
Ezzat, S.	2002	42	6	42	46.5 (12.1)	115	EF, FM, IGF1, IGFBP3, LBM, TBW, WHR	0
Smith, J.C.	2002	43	6	41	43.0 (12.5)	64	DBP, HR, SBP	0
Sneppen, S.B.	2002	44	18	50	39.0 (ND)	20	EAR, FS	2
Brammert, M.	2003	45	6	37	42.0 (2.6)	19	BMI, Fasting Glucose, Fasting Insulin, IGF1, IGF1SDS, TBW	0
Chihara, K.	2004	47	6	52	38.0 (8.4)	64	IGF1, IGF1SDS, IGFBP3SDS, LBM, LDL, Tchol	0
Bell, W.	2004	46	6	47	44.1 (7.3)	43	BMI, DBP, HDL, LDL, SBP, Tchol, TG, TRG, WHR	0
Christ, E.R.	2004	37	3	54	49.5 (ND)	13	FM, HDL, HgbA1c, LBM, LDL, Tchol	0
Hoffman, A.R.	2004	50	12	48	48.2 (ND)	166	Fasting Glucose, LBM, HgbA1c	35
Elgzyri, T.	2004	49	6	19	68.0 (ND)	31	EAR, FS, HR	3
Dutta, P.	2010	57	3	0	47 (3.9)	26	BMI, FM, IGF1, LDL, HDL, TG, Tchol, Fasting Glucose	0
Chihara, K.	2006	52	6	37	37.2 (13.0)	73	FM, HDL, IGF1, IGF1SDS, IGFBP3, IGFBP3SDS, LBM, LDL, Tchol	5
Bollerslev, J.	2006	51	9	44	49.0 (ND)	55	CRP, HDL, LDL, Tchol, TG	7
Chihara, K.	2008	54	6	42	37.2 (ND)	116	FM, HDL, IGF1SDS, IGFBP3SDS, LBM, LDL, Tchol, TG, TRF	0
Beauregard, C.	2008	53	6	100	46.2 (ND)	43	CRP, Fasting Glucose, Fasting Insulin, FFM, FM, HDL, IGF1, IGF1SDS, LDL, Tchol, TG, WHR	0
Cittadini, A.	2009	55	6	16	62.0 (2.5)	56	DBP, EF, Fasting Glucose, HR, IGF1, LVM, SBP, Tchol, TG	0
Miller, K. K.	2010	58	6	50	46.8 (12.3)	30	CRP, Fasting Glucose, Fasting Insulin, FFM, FM, HDL, HgbA1c, IGF1SDS, LDL, Tchol, TG	0
Whitehead, H.M.	1992	18	6	36	29.4 (2.7)	10	Fasting Glucose, FM, LBM, Tchol	4
Chihara, K.	2010	56	6	51	33.5 (12.0)	94	IGFBP3SDS, LDL, Tchol	0
Newman, C.B.	2010	59	6	45	46.6 (0)	30	EAR, EF, FM, FS, HDL, LBM, LDL, LVM, Tchol, TG, SV	0
Russell-Jones, D.L.	1993	20	2	55	46.6 (2.2)	18	Fasting Insulin, IGF1, LBM	0
Florkowski, C.M.	1996	60	3	0	47.0 (ND)	20	BMI, WHR	0
Beshyah, S.A.	1995	61	6	53	44.0 (ND)	40	LBM, WHR	0
Johannsson, G.	1996	62	6	35	44.3 (1.2)	68	BMI, FM, IGF1, TBW	3
Snel, Y.E.	1995	63	6	44	ND	25	BMI, FFM, FM	13
Mesa, J.	2003	64	6	36	36.6 (11.5)	165	BMI, FFM, FM, IGF1, IGFBP3, TBW, WHR	
Sattler, F.R.	2009	13	4	0	70.3 (4.2)	37	FM, LBM	
Blackman, M.R.	2002	14	6	44	71.0 (1.2)	131	FM, LBM	

IGF1: insulin-like growth factor 1; IGFBP3: insulin-like growth factor binding protein 3; WHR: waist-to-hip ratio; LBM: lean body mass; FFM: fat free mass; TrF: trunk fat; TBW: total body water; FM: fat mass; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; SV: stroke volume; LDL: low density lipoprotein; HDL: high density lipoprotein; Tchol: total cholesterol; TG: triglycerides; ApoB: apolipoprotein B; CRP: C-reactive protein; EAR: E/A ratio; FS: fractional shortening; LVM: left ventricular mass; HgbA1c: hemoglobin A1c; SD: standard deviation.

3.1. Growth Hormone Serum Parameters

Data for serum parameters evaluating GH administration were obtained from 19 studies involving 983 patients. Significant positive effects on IGF-1, a surrogate marker for GH used primarily due to its significantly longer half-life, and IGFBP3, a major IGF binding protein that is used to assess GH production in concert with IGF-1, were observed (**Table 2, Figure 2**). Due to lack of standardization of IGF-1 levels to age across all studies, a comprehensive z-score analysis that accounts for the effects of GH as a function of age could not be performed. The above data are in line with other studies demonstrating an increase in serum IGF-1 and IGFBP3 as a result of GH administration [40,42,52].

3.2. Anthropomorphic Parameters

Growth hormone enhances lean body mass through skele-

tal muscle growth stimulation and fat loss [24,28,39]. We extracted data for waist-hip ratio (WHR), lean body mass (LBM)/fat free mass (FFM), trunk fat (TrF), total body water (TBW), fat mass (FM), and body mass index (BMI) from 28 studies involving 1464 patients (**Table 2, Figure 2**). Significant negative effects of GH administration were observed for WHR and FM, and significant positive effects observed for LBM, FFM, and TBW. No significant effects of GH administration were observed on TrF and BMI. Sensitivity analysis, in which the study with the largest patient population for each variable was removed from the analysis, demonstrated no significant changes in ES for all variables (**Supplementary Table 1**).

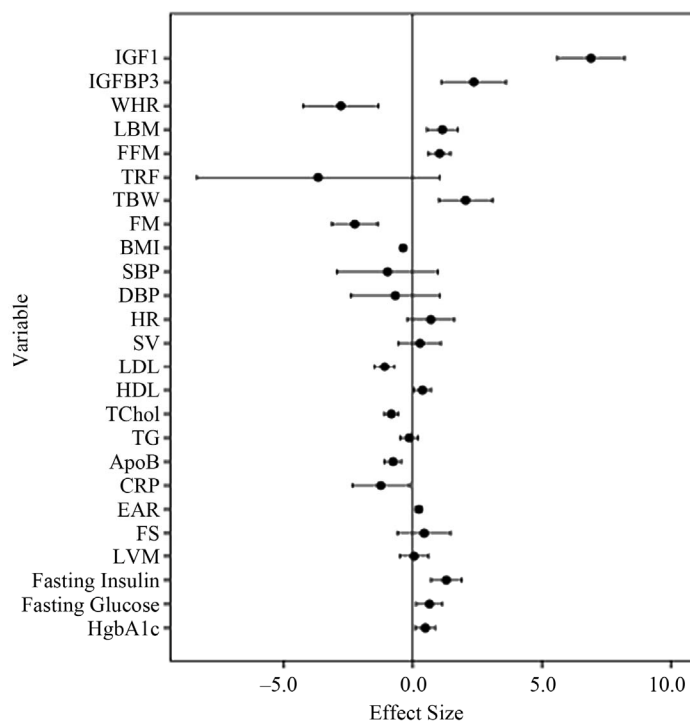
3.3. Cardiovascular Parameters

Given that GHD is associated with depressed systolic heart function and increased CV mortality, understanding

Table 2. Summary analysis of all variables.

Variable	# Studies	Total Subjects	# Drug Subjects	# Placebo Subjects	WMD (SD)	Q	ES	ES P-Value	ES 95% CI
IGF1	19	983	496	487	81.62 (1.84) ng/mL	0.00	6.90	<0.0001	5.58, 8.21
IGFBP3	5	529	268	261	0.55 (0.09) ng/mL	0.00	2.36	0.0002	1.11, 3.61
WHR	8	587	296	291	-0.03 (0.08)	0.00	-2.79	0.0002	-4.25, -1.32
LBM	15	755	384	371	1.17 (0.08) kg	0.00	1.15	0.0002	0.55, 1.74
FFM	6	451	225	226	0.95 (0.10) kg	0.00	1.04	<0.0001	0.62, 1.46
TrF	3	183	93	90	-1.80 (0.18) kg	0.00	-3.67	0.1256	-8.37, 1.04
TBW	7	568	287	281	0.92 (0.09) L	0.00	2.04	0.0001	1.00, 3.08
FM	17	872	445	427	-1.35 (0.08) kg	0.00	-2.25	<0.0001	-3.15, -1.35
BMI	10	412	211	201	-0.05 (0.10) kg/m ²	0.89	-0.38	<0.0001	-0.44, -0.32
SBP	5	344	169	175	-1.77 (0.13) mmHg	0.00	-0.98	0.3268	-2.94, 0.98
DBP	5	344	169	175	-1.60 (0.12) mmHg	0.00	-0.68	0.4389	-2.40, 1.04
HR	5	207	102	105	0.61 (0.14) BPM	0.00	0.70	0.1327	-0.21, 1.61
SV	3	104	51	53	-0.49 (0.24) mL	0.05	0.28	0.5092	-0.55, 1.10
LDL	23	1045	524	521	-8.07 (0.20) mg/dL	0.00	-1.09	<0.0001	-1.49, -0.70
HDL	21	918	460	458	0.97 (0.07) mg/dL	0.00	0.37	0.032	0.03, 0.71
TChol	26	1139	572	567	-7.09 (0.16) mg/dL	0.00	-0.83	<0.0001	-1.12, -0.54
TG	21	961	481	480	-1.22 (0.07) mg/dL	0.00	-0.14	0.4225	-0.49, 0.2
ApoB	3	82	41	41	-0.12 (0.22) g/L	0.52	-0.76	<0.0001	-1.09, -0.44
CRP	4	223	110	113	-1.02 (0.14) mg/L	0.00	-1.24	0.0284	-2.35, -0.13
EAR	5	137	66	71	0.02 (0.17)	0.75	0.23	<0.0001	0.13, 0.34
FS	6	145	71	74	0.68 (0.17) %	0.00	0.44	0.4036	-0.59, 1.47
LVM	6	186	91	95	-0.96 (0.16) g	0.00	0.05	0.8633	-0.52, 0.62
Fasting Insulin	12	454	228	226	1.63 (0.11) μ IU/mL	0.00	1.30	0.0001	0.69, 1.91
Fasting Glucose	15	480	242	238	1.60 (0.08) mg/dL	0.00	0.64	0.0144	0.13, 1.16
HgbA1c	7	446	227	219	0.05 (0.10) %	0.01	0.48	0.0155	0.09, 0.87

#Studies: number of studies in which a given variable was assessed; WMD: weighted mean difference; SD: standard deviation; Q: Q parameter; ES: effect size; CI: -95% confidence interval.



IGF1: insulin-like growth factor 1; IGFBP3: insulin-like growth factor binding protein 3; WHR: waist-to-hip ratio; LBM: lean body mass; FFM: fat free mass; TrF: trunk fat; TBW: total body water; FM: fat mass; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; SV: stroke volume; LDL: low density lipoprotein; HDL: high density lipoprotein; TChol: total cholesterol; TG: triglycerides; ApoB: apolipoprotein B; CRP: C-reactive protein; EAR: E/A ratio; FS: fractional shortening; LVM: left ventricular mass; HgbA1c: hemoglobin A1c.

Figure 2. Forest plot of effect sizes for all variables assessed.

whether GH replacement improves heart function and decreases mortality risk is essential [67,68]. We extracted data assessing systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), stroke volume (SV), LDL, HDL, total cholesterol (TChol), total triglycerides (TG), apolipoprotein B (ApoB), C-reactive protein (CRP), the early to late ventricular diastolic filling (E/A) ratio (EAR), left ventricular mass (LVM) and left ventricular fractional shortening (FS) from 33 studies involving 1269 patients (**Table 2, Figure 2**). Significant negative effects of GH administration were observed on LDL, TChol, ApoB, and CRP, and a small but significant positive effect was seen on EAR and HDL cholesterol. No effect was observed for SBP, DBP, HR, SV, TG, LVM, or FS.

Sensitivity analysis demonstrated significant positive effects for SV and HR, and no significant change in EAR and CRP, indicating that the contributions of individual studies were significant in the determination of our initial results (**Supplementary Table 1**). While our results with regards to the effects of GH on LDL and TChol are in line with those of a prior meta-analysis, we find no significant decrease in DBP in our study, in contrast with prior findings [9]. In addition, while a prior meta-analysis had identified an increase in SV as a function of GH

administration, we find no significant effect on SV in our analysis, except when excluding the largest study analyzing SV, which evaluated 30 patients of a total of 104 evaluated for SV in our analysis (**Supplementary Table 1**) [10,59].

3.4. Carbohydrate Metabolism

GH is known to impair glucose tolerance and antagonize insulin action through an incompletely defined mechanism [69]. Data from 19 studies involving 913 patients were analyzed, demonstrating that GH produces a significant increase in fasting insulin, glucose and HgbA1c (**Table 2, Figure 2**). These data are largely in agreement with those of prior studies. However, while our analysis demonstrates a significant increase in HgbA1c, numerous included studies found no change in HgbA1c levels [41,52]. A sensitivity analysis demonstrated no change in significance of ESs across assayed variables (**Supplementary Table 1**) [23,28,33].

3.5. Sex Steroids

Evaluation for hypogonadism and subsequent T replacement is commonplace in the aging male population,

whereas testing for GHD is far less common. In addition, in individuals using anabolic steroids, it is of interest to assess whether the use of GH can offset potentially deleterious CV effects associated with steroid use, including increased LDL, decreased HDL, elevated SBP and DBP, and changes in cardiac electrophysiology and left ventricular size [70]. However, few controlled studies exist assessing the role of GH administration in the setting of T replacement. We identified 2 randomized, placebo-controlled studies involving 184 patients comparing T replacement to GH and T or GH replacement to placebo and performed a nested meta-analysis of FM and LBM, the only common variables assessed by these studies. We observed a significant negative effect of GH on FM and a significant positive effect on LBM in comparison to placebo, in agreement with our larger analysis above (Table 3). When comparing administration of GH and T simultaneously with administration of T alone, we observed a significant negative effect of GH and T on FM but not on LBM. Finally, when comparing simultaneous GH and T administration to GH alone, we observe no significant effect of the combination on FM or LBM. Taken together these data suggest that GH has a more pronounced effect on FM and LBM than T.

3.6. Effect of GH Dose

To better define the effects of GH dose, we meta-analyzed studies segregated based on a GH dose cutoff of 0.35 U/kg/week. We analyzed 37 studies involving 1788 patients that utilized a GH dose of <0.35 U/kg/week (low dose), and 11 studies involving 443 patients that utilized a GH dose of ≥ 0.35 U/kg/week (high dose), and find that a high dose of GH results in a significantly greater effect on FS compared to low dose GH ($P = 0.012$) (Supplementary Table 2).

3.7. Effect of Gender

In order to define the effects of gender, we performed meta-analysis using a cutoff of 50% of females in any

given study. Using these criteria, we analyzed 30 studies involving 1713 patients with <50% females and 18 studies involving 518 patients with $\geq 50\%$ females, and find no significant differences between variables as a function of gender (Supplementary Table 3).

3.8. Effect of Treatment Duration

To compare the effects of GH as a function of treatment duration, we meta-analyzed studies using a cutoff of 6 months duration (Supplementary Table 4). We included 10 studies involving 176 patients of <6 months duration and 38 studies involving 2055 patients of ≥ 6 months duration. We observe a significantly greater negative effect of GH administration on BMI ($P = 0.03$) in patients treated for ≥ 6 months.

3.9. Effect of Age

To compare the effects of GH as a function of subject age, we meta-analyzed studies using a cutoff of 40 years of age in order to have sufficient data for analysis in both groups. Using this criterion, we included 14 studies involving 819 patients <40 years old and 34 studies involving 1412 patients ≥ 40 years old. We find no significant differences between variables as a function of age (Supplementary Table 5).

4. Discussion

Growth hormone has been used for treatment of GHD since 1958, when it was first purified from human pituitary glands. In the 1980s, recombinant GH became available and permitted widespread treatment of GHD, prompting study of the GHD population [8]. Since the most recent meta-analysis that evaluated CV, carbohydrate, and lipid parameters, numerous randomized, controlled studies evaluating the effects of GH have been published. Our goal was to update the literature with regards to the GH effect in the above parameters through meta-analysis of randomized, controlled trials.

Table 3. Nested meta-analysis of studies assessing concomitant sex steroid and GH administration.

GH + Testosterone vs. Placebo						
Variable	# Studies	# Subjects	ES	P-Value	WMD (SD)	
FM	2	184	-2.81	<0.0001	-2.46 (0.35) kg	
LBM	2	184	2.21	0.0417	2.11 (0.33) kg	
GH + Testosterone vs. Testosterone						
FM	2	184	-1.83	<0.0001	-1.96 (0.32) kg	
LBM	2	184	1.91	0.1223	1.58 (0.30) kg	
GH + Testosterone vs. GH						
FM	2	184	-0.55	0.2915	-1.10 (0.28) kg	
LBM	2	184	0.55	0.3859	0.89 (0.28) kg	

ES: effect size; WMD: weighted mean difference; SD: standard deviation.

4.1. Growth Hormone Serum Effects

In most included studies baseline IGF-1 and IGFBP3 levels were <100 ng/mL, with a significant increase in serum IGF-1 levels of ~81 ng/mL after GH administration (**Table 2**). This is in line with prior data, which demonstrate a 1-3 fold increase in IGF-1 levels after 6 - 12 months of GH therapy [24,25,30,32,33]. GH therapy is also associated with increased serum insulin binding protein levels, specifically IGFBP3, which is in line with our findings [71,72]. However, the effects of GH on levels of other IGFBPs are not well established and of studies that have evaluated the relationship between GH and these other IGFBPs, no correlation has been observed [42,73].

4.2. Anthropomorphic and CV Effects

GHD in adults is associated with increased vascular mortality rates [19,22]. Previous studies have attributed this trend to adverse effects on anthropomorphic and CV parameters such as increased total cholesterol, LDL, WHR, and adiposity and decreased HDL [3,7,19,32]. In our analysis, we observed improvement in several of these parameters after GH administration, with increases in both LBM and FFM, and a decrease in the WHR. No significant change in body weight was found regardless of the modality used to assess these variables. Decreases in LDL, TChol, ApoB, and CRP, and an increase in HDL were also observed. Most studies that assessed these variables were 6 months long, with several of 12 months duration (**Table 1**) [12,18,41,46,48,52-54,58,59,67]. Approximately half of the included studies find an increase in HDL (3 of 8) and/or decrease in LDL (5 of 9), whereas the majority of studies find a decrease in TChol (7 of 9), and no studies find a change in TG (7 of 7). Two studies found the decrease in LDL and total cholesterol to be transient, limited to the first 3 - 12 months of therapy [31, 41]. We observe significant ESs for LDL, HDL, and TChol in our analysis, which coincides with the results of the most recent meta-analysis to evaluate serum lipids in the setting of GH administration, though in that study the change in HDL was not statistically significant [9]. Mechanistically, GH increases hepatic uptake of very low density lipoprotein (VLDL) cholesterol and this may decrease conversion of VLDL to LDL, potentially explaining the above effect [74]. The effect of GH treatment duration on serum lipids is a debated topic. We observed no significant differences in LDL, TChol, or HDL when assessing the effects of GH treatment duration. However this may be due to the lack of studies of longer than 12 months duration.

We find no change in SBP, DBP, HR, SV, LVM, or FS, and a small, but significant positive effect on the EAR resulting from increases in EAR in 2 studies [21,25].

These findings echo those of a prior meta-analysis for SBP, though a significant decrease in DBP was demonstrated in that study, which is not recapitulated in our study [9]. Other non-placebo controlled studies not included in this analysis have shown a statistically significant moderate increase in systolic and diastolic blood pressure secondary to GH treatment [75,76]. These differences in effect on BP may be secondary to mechanism of measurement, specifically ambulatory monitoring vs. conventional sphygmomanometer. A recent controlled trial of GH administration using 0.26 U/kg/wk of GH demonstrated no changes in EAR, SV, or FS [59]. In contrast, an earlier study used 0.35 U/kg/wk of GH and demonstrated increases in EAR, SV, and FS [25]. Studies utilizing GH doses of 0.10 - 0.20 U/kg/week demonstrated no changes in EAR or FS, supporting previous conclusions that the CV effects of GH are likely related to dose [44,49], which is also supported by the finding that acromegaly results in increased CV mortality [77]. Earlier studies using higher GH doses demonstrated increases in LVM and other echocardiographic indices of heart function [25,78], whereas more recent studies using lower GH doses demonstrate no changes in these indices, suggesting that lower dose GH regimens are safer for cardiac function [18,24,25,79]. These data suggest that GH administration in low to moderate doses results in normalization of cardiac performance and may have cardioprotective effects in patients with GHD, who have a 1.9-fold increased risk of CV mortality [68]. Notably, GH has been shown to normalize nitric oxide production when administered to GHD individuals, suggesting a molecular mechanism for enhanced cardiac performance, as well as cardioprotection [26]. However a recent uncontrolled 12-month trial of GH treatment concluded that GH increases carotid intima media thickness (IMT), ultimately leading to an increased number of atherosclerotic plaques [80]. In our analysis, only one study included IMT as an endpoint, in which the result was not significant. Longer duration studies are necessary to determine whether these changes have an overall effect on CV mortality.

4.3. Carbohydrate Metabolism

GH therapy has been implicated in development of insulin resistance and type II diabetes [69]. Our data show that GH produces a significant increase in fasting insulin and fasting glucose, which is likely related to GH's insulin antagonizing effect [29,69]. The incidence of diabetes among the studies we analyzed was variable, though no studies reported new diagnoses of diabetes as a result of GH administration despite reporting increases in fasting insulin and glucose levels that potentially signify insulin resistance. Notably, few studies discussed diabetes in the

context of increased insulin and glucose levels, making it difficult to assess whether diabetes was affected by GH treatment.

Insulin resistance due to GH may be a transient effect that subsides within 3 - 6 months of the onset of GH therapy, as normalization of insulin-mediated glucose disposal in the setting of persistently elevated fasting insulin and C-peptide levels after 3 months of GH treatment has been observed [81]. These results have been reproduced by others [23,82], and reports supporting the conclusion that GHD induces a state of insulin resistance that is then normalized by GH administration are also available [29, 83]. A recent study conducted over 4 years concluded that there was no evidence of increased DM incidence in GHD patients on GH treatment [84]. However, more recent studies have demonstrated a persistent state of insulin resistance through 6 months of GH treatment that is linked to a switch from glucose clearance to lipid oxidation [45]. In addition, we find a small, significant increased effect on HgbA1c, which further supports a role for persistent dysregulation of glucose metabolism by GH. Given that most studies of GH administration do not go past 18 months, the long-term effects of GH administration on glucose metabolism bear additional study, particularly in the setting of a 6-fold increase in type 2 diabetes in children treated with GH [69].

4.4. Safety

The long-term safety of GH administration remains unclear, as most studies evaluate the safety profiles of GH administration over only 6 - 18 months. Lower dose GH therapy appears to be safer in the short term from the CV perspective, as described above, although the long-term CV and stroke risk in GH-treated patients remains unknown. A recent observational study in 281 patients with ischemic stroke demonstrated a minimal contribution of GH to the risk of poor functional outcome and death in these patients [85]. However, a study in female rats demonstrated that low IGF-1 levels increased the contribution of estrogen to ischemic stroke risk, suggesting that GHD may contribute to stroke risk in humans [86]. In addition, no controlled studies exist examining the use of GH with anabolic steroids in individuals without GHD, and thus the safety and efficacy of GH use in this population remains unclear [87]. Our study was unable to effectively assess adverse effects of GH treatment, as only 5 of the 48 studies utilized included such data.

4.5. Study Limitations

While this meta-analysis attempted to account for possible variations in effect size through an assessment of treatment duration, GH treatment dose, gender, and age, one important factor that is missing is the onset of GHD.

Previous studies have observed differences in IGF-1 level and response between childhood and adult onset GHD subjects, specifically that childhood onset GHD adults have a lower baseline IGF-1 level and a greater improvement in quality of life [88,89]. However in our analysis, only 3 studies included information on timing of GHD onset [27,47,56]; this subject was therefore not included in the subgroup analysis.

4.6. Future Directions

Our data argue that GH treatment in the setting of GHD results in positive changes in anthropomorphic indices, as well as beneficial changes in CV parameters. However the long-term risk of stroke and myocardial infarction rates related to GH administration are unknown and will need to be determined in future studies. While GH therapy appears to negatively affect insulin and glucose metabolism, whether this results in development of diabetes mellitus remains an unanswered question. Furthermore, no safety or efficacy data are available for GH administration in the non-GHD population, and very limited data exist on the interaction between GH and testosterone. Finally, while the risk of malignancy resulting from GH administration appears low, the true long-term effects of GH therapy on malignancy need to be further elucidated, and multiple additional populations assessed. Further work should focus on these unanswered questions with regard to GH administration.

4.7. Conclusion

GH treatment in GHD adults results in beneficial effects on total cholesterol, LDL, HDL, ApoB, CRP, LBM, FFM and WHR. As expected, GH reduces insulin sensitivity with increases in fasting insulin, fasting glucose and HgbA1C. Data on long-term safety, including on CV effects, insulin sensitivity and malignancy, as well as data assessing the role of GH replacement in combination with testosterone replacement needs to be assessed in larger, long-term trials.

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Supplementary Tables

Supplementary Table 1. Summary of sensitivity analysis.

Variable	Study Excluded (Reference)	Population of Study Excluded	Initial P-Value	Post P-Value	Initial ES	Post ES
IGF1	64	165	<0.0001	<0.0001	6.90	7.34
IGFBP3	64	165	0.0002	0.0012	2.36	2.80
WHR	64	165	0.0002	0.0008	-2.79	-3.42
LBM	50	166	0.0002	0.001	1.15	1.14
FFM	64	165	<0.0001	0.0012	1.04	0.99
TRF	54	116	0.1265	0.1761	-3.67	-0.31
TBW	64	165	0.0001	0.0011	2.04	1.98
FM	64	165	<0.0001	<0.0001	-2.25	-2.08
BMI	64	165	<0.0001	0.021	-0.38	-0.16
SBP	32	163	0.3268	0.786	-0.98	-0.23
DBP	32	163	0.4389	0.8039	-0.68	0.12
HR	43	64	0.1327	0.0044	0.70	1.03
SV	59	30	0.5092	<0.0001	0.28	0.72
LDL	51	55	<0.0001	<0.0001	-1.09	-1.14
HDL	51	55	0.032	0.0392	0.37	0.39
TChol	32	163	<0.0001	<0.0001	-0.83	-0.82
TG	32	163	0.4225	0.2136	-0.14	-0.21
ApoB	23	40	<0.0001	0.0009	-0.76	-0.96
CRP	51	55	0.0284	0.0703	-1.24	-1.57
EAR	21	36	<0.0001	0.1621	0.23	0.21
FS	49	31	0.4036	0.4106	0.44	0.44
LVM	55	56	0.8633	0.1367	0.05	0.24
Fasting Insulin	27	165	<0.0001	<0.0001	1.30	1.43
Fasting Glucose	27	165	0.0144	0.0305	0.64	0.66
HgbA1c	27	165	0.0155	0.0088	0.48	0.65

ES: effect size.

Supplementary Table 2. Meta-analysis of studies by GH dose.

Variable	Low Dose GH (<0.35 U/kg/week)					High Dose GH (≥0.35 U/kg/week)				
	# Studies	# Subjects	ES	P-Value	WMD (SD)	# Studies	# Subjects	ES	P-Value	WMD (SD)
IGF1	17	949	6.51	<0.0001	78.97 (1.83) ng/mL	2	52	9.97	<0.00001	129.08 (12.66) ng/mL
IGFBP3	5	547	2.36	0.0002	0.55 (0.09) ng/mL	0	0	ND	ND	ND
WHR	7	565	-3.31	0.0001	-0.03 (0.09)	1	40	ND	ND	ND
LBM	11	505	1.36	0.0018	1.03 (0.1) kg	4	240	0.67	0.0387	1.50 (0.16) kg
FFM	6	469	1.04	<0.0001	0.95 (0.1) kg	0	0	ND	ND	ND
TRF	2	159	-5.24	0.3053	-1.81 (0.19) kg	1	24	ND	ND	-1.77 (0.48) kg

Continued

TBW	7	287	2.04	0.0001	0.92 (0.09) L	0	0	ND	ND	ND
FM	15	828	-2.44	<0.0001	-1.28 (0.08) kg	2	34	-0.88	0.0356	-2.47 (0.37) kg
BMI	10	412	-0.38	0.0004	-0.05 (0.1) kg/m ²	0	0	ND	ND	ND
SBP	4	326	-1.82	0.0526	-2.54 (0.15) mmHg	1	36	ND	ND	4.83 (0.66) mmHg
DBP	4	326	-1.32	0.1298	-2.01 (0.14) mmHg	1	36	ND	ND	1.89 (0.4) mmHg
HR	3	151	0.54	0.4115	0.39 (0.16) BPM	2	56	1	0.2992	1.21 (0.29) BPM
SV	1	30	ND	ND	ND	2	44	0.72	<0.00001	2.45 (0.4) mL
LDL	19	916	-1.00	<0.0001	-7.29 (0.19) mg/dL	4	123	-1.67	0.0263	-13.36 (0.87) mg/dL
HDL	17	758	0.36	0.0474	1.00 (0.08) mg/dL	4	123	0.48	0.4422	0.78 (0.19) mg/dL
TChol	21	990	-0.76	<0.0001	-6.44 (0.16) mg/dL	5	133	-1.24	0.0273	-11.34 (0.67) mg/dL
TG	17	801	-0.21	0.3054	-1.98 (0.09) mg/dL	4	123	0.13	0.7005	3.80 (0.3) mg/dL
ApoB	1	18	ND	ND	ND	2	64	-0.69	<0.00001	-0.14 (0.25) g/L
CRP	4	168	-1.24	0.0284	-1.02 (0.14) mg/L	0	0	ND	ND	ND
EAR	3	81	0.04	0.8892	-0.01 (0.22)	2	56	0.44	0.1036	0.07 (0.27)
FS	4	101	-0.3	0.0908	0.26 (0.2) %	2	44	1.81	0.005	1.66 (0.35) %
LVM	3	106	-0.27	0.5421	-2.55 (0.26) g	3	80	0.35	0.2081	1.14 (0.24) g
Fasting Insulin	10	390	1.21	0.0001	1.62 (0.12) μ IU/mL	2	64	1.65	0.145	1.69 (0.29) μ IU/mL
Fasting Glucose	11	588	0.71	0.0542	1.22 (0.09) mg/dL	4	240	0.42	0.0115	2.53 (0.18) mg/dL
HgbA1c	6	280	0.61	0.0273	0.06 (0.12) %	1	166	ND	ND	0.07 (0.18) %

ES: effect size; WMD: weighted mean difference; SD: standard deviation.

Supplementary Table 3. Meta-analysis of studies by gender.

Variable	<50% Females					\geq 50% Females				
	# Studies	# Subjects	ES	P-Value	WMD (SD)	# Studies	# Subjects	ES	P-Value	WMD (SD)
IGF1	12	788	7.93	<0.0001	82.92 (2.11) ng/mL	7	213	5.15	<0.0001	76.89 (3.73) ng/mL
IGFBP3	5	547	2.36	0.0002	0.55 (0.09) ng/mL	0	0	ND	ND	ND
WHR	5	506	-3.96	0.0002	-0.03 (0.09)	3	99	-1.27	0.1755	-0.01 (0.2)
LBM	9	585	1.47	0.0013	1.16 (0.09) kg	6	160	0.70	0.0018	1.22 (0.17) kg
FFM	4	396	1.31	<0.0001	1.07 (0.11) kg	2	73	0.47	0.2658	0.30 (0.24) kg
TRF	3	183	-3.67	0.1265	-1.80 (0.18) kg	0	0	ND	ND	ND
TBW	6	280	2.26	0.0001	0.90 (0.09) L	1	7	ND	ND	1.53 (0.63) L
FM	11	683	-2.64	<0.0001	-1.38 (0.09) kg	6	179	-1.53	0.0021	-1.26 (0.16) kg
BMI	8	384	-0.13	0.0997	-0.05 (0.10) kg/m ²	2	28	-0.08	0.1726	0.01 (0.38) kg/m ²
SBP	4	326	-1.82	0.0526	-2.54 (0.15) mmHg	1	36	ND	ND	4.83 (0.66) mmHg
DBP	4	326	-1.32	0.1298	-2.01 (0.14) mmHg	1	36	ND	ND	1.89 (0.4) mmHg
HR	4	171	0.87	0.1451	0.69 (0.16) BPM	1	36	ND	ND	0.25 (0.34) BPM
SV	3	74	0.28	0.5092	-0.49 (19.02) mL	0	0	ND	ND	ND
LDL	11	659	-1.22	0.0001	-9.05 (0.28) mg/dL	12	398	-0.98	0.0003	-6.55 (0.26) mg/dL
HDL	11	629	0.32	0.0666	0.90 (0.09) mg/dL	10	270	0.44	0.2605	1.14 (0.14) mg/dL

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TChol	14	669	-0.83	<0.0001	-6.86 (0.19) mg/dL	12	428	-0.83	0.0032	-7.55 (0.29) mg/dL
TG	11	695	-0.05	0.8002	-1.07 (0.08) mg/dL	9	239	-0.27	0.4903	-1.68 (0.15) mg/dL
ApoB	1	24	ND	ND	-0.19 (0.41) g/L	2	58	-0.87	0.0065	-0.10 (0.26) g/L
CRP	2	95	-0.44	0.0005	-0.99 (0.17) mg/L	2	73	-2.15	0.1270	-1.10 (0.25) mg/L
EAR	3	81	0.27	0.1135	0.01 (0.22)	2	56	0.21	0.0580	0.03 (0.27)
FS	5	125	0.67	0.2964	0.87 (0.19) %	1	20	ND	ND	-0.45 (0.45) %
LVM	5	150	0.10	0.7894	-0.48 (0.17) g	1	36	ND	ND	3 (0.49) g
Fasting Insulin	6	297	1.23	0.0071	1.63 (0.13) μ IU/mL	6	157	1.39	0.0023	1.61 (0.18) μ IU/mL
Fasting Glucose	9	687	0.91	0.0156	2.02 (0.10) mg/dL	5	141	0.36	0.3113	0.68 (0.17) mg/dL
HgbA1c	4	389	0.34	0.1474	0.05 (0.11) %	3	57	0.74	0.0077	0.10 (0.27) %

ES: effect size; WMD: weighted mean difference; SD: standard deviation.

Supplementary Table 4. Meta-analysis of studies by study duration.

Variable	<6 months					\geq 6 months				
	# Studies	# Subjects	ES	P-Value	WMD (SD)	# Studies	# Subjects	ES	P-Value	WMD (SD)
IGF1	3	56	9.04	0.0307	106.6 (10.08) ng/mL	16	945	6.75	<0.0001	80.11 (1.86) ng/mL
IGFBP3	0	0	ND	ND	ND	5	547	2.36	0.0002	0.55 (0.09) ng/mL
WHR	1	20	ND	ND	ND	7	585	-3.25	0.0001	-0.03 (0.08)
LBM	5	80	0.43	0.0001	1.52 (0.26) kg	10	665	1.44	0.0003	1.13 (0.09) kg
FFM	0	0	ND	ND	ND	6	469	1.04	<0.0001	0.95 (0.10) kg
TRF	1	24	ND	ND	ND	2	159	-5.24	0.3053	-1.81 (0.19) kg
TBW	1	13	ND	ND	ND	6	573	2.26	0.0001	0.9 (0.09) L
FM	4	76	-0.47	0.0082	-1.51 (0.26) kg	13	786	-2.74	<0.0001	-1.34 (0.08) kg
BMI	3	58	0.31	<0.0001	0.08 (0.26) kg/m ²	7	354	-0.28	<0.0001	-0.07 (0.11) kg/m ²
SBP	0	0	ND	ND	ND	5	362	-0.98	0.3268	-1.77 (0.13) mmHg
DBP	0	0	ND	ND	ND	5	362	-0.68	0.4389	-1.6 (0.12) mmHg
HR	0	0	ND	ND	ND	5	207	0.70	0.1327	0.61 (0.14) BPM
SV	0	0	ND	ND	ND	3	74	0.28	0.5092	-0.49 (0.24) mL
LDL	5	89	-1.66	<0.0001	-11 (0.86) mg/dL	18	792	-0.94	<0.0001	-7.77 (0.2) mg/dL
HDL	5	89	0.46	0.1144	0.76 (0.22) mg/dL	16	950	0.36	0.0740	1.00 (0.08) mg/dL
TChol	5	89	-1.07	<0.0001	-7.75 (0.63) mg/dL	21	1034	-0.81	<0.0001	-7.04 (0.17) mg/dL
TG	4	76	-0.06	0.9092	0.69 (0.24) mg/dL	17	848	-0.16	0.4166	-1.39 (0.08) mg/dL
ApoB	1	18	ND	ND	ND	2	64	-0.69	<0.0001	-0.14 (0.25) g/L
CRP	0	0	ND	ND	ND	4	168	-1.24	0.0284	-1.02 (0.14) mg/L
EAR	0	0	ND	ND	ND	5	137	0.23	<0.0001	0.02 (0.17)
FS	0	0	ND	ND	ND	6	145	0.44	0.4036	0.68 (0.17) %
LVM	0	0	ND	ND	ND	6	186	0.05	0.8633	-0.96 (0.16) g
Fasting Insulin	4	68	1.33	0.0006	1.95 (0.29) μ IU/mL	8	386	1.28	0.0013	1.57 (0.12) μ IU/mL
Fasting Glucose	3	62	-0.19	0.8326	0.61 (0.26) mg/dL	12	766	0.83	0.0026	1.69 (0.09) mg/dL
HgbA1c	2	27	1.21	<0.0001	0.13 (0.4) %	5	419	0.34	0.0864	0.06 (0.10) %

ES: effect size; WMD: weighted mean difference; SD: standard deviation.

Supplementary Table 5. Meta-analysis of studies by subject age.

Variable	<40 years					≥40 years				
	# Studies	# Subjects	ES	P-Value	WMD (SD)	# Studies	# Subjects	ES	P-Value	WMD (SD)
IGF1	5	348	3.92	<0.0001	86.58 (3.28) ng/mL	14	653	8.44	<0.0001	78.90 (2.22) ng/mL
IGFBP3	2	238	1.06	0.0002	0.61 (0.13) ng/mL	3	309	3.33	0.0119	0.5 (0.12) ng/mL
WHR	2	181	-0.91	0.0031	-0.02 (0.15)	6	424	-3.91	0.0007	-0.03 (0.1)
LBM	5	287	2.15	0.0208	1.12 (0.13) kg	10	458	0.77	0.0000	1.22 (0.11) kg
FFM	1	165	ND	ND	ND	5	279	0.99	0.0012	0.92 (0.14) kg
TRF	2	140	-5.48	0.2599	-2.3 (0.22) kg	1	43	ND	ND	ND
TBW	1	165	ND	ND	ND	6	421	1.98	0.0011	0.88 (0.1) L
FM	7	468	-2.52	0.0024	-1.4 (0.10) kg	10	329	-2.04	0.0002	-1.29 (0.11) kg
BMI	2	181	-0.09	0.9131	0.08 (0.15) kg/m ²	8	371	-0.23	0.0019	-0.15 (0.13) kg/m ²
SBP	0	0	ND	ND	ND	5	362	-0.98	0.3268	-1.77 (0.13) mmHg
DBP	0	0	ND	ND	ND	5	362	-0.68	0.4389	-1.6 (0.12) mmHg
HR	0	0	ND	ND	ND	5	207	0.70	0.1327	0.61 (0.14) BPM
SV	1	24	ND	ND	ND	2	50	0.05	0.9342	-1.69 (0.33) mL
LDL	7	420	-0.63	0.0235	-7.18 (0.28) mg/dL	16	619	-1.30	<0.0001	-8.64 (0.27) mg/dL
HDL	5	259	0.43	0.3172	1.44 (0.14) mg/dL	16	622	0.37	0.0643	0.78 (0.08) mg/dL
TChol	8	427	-0.48	0.0184	-7.66 (0.29) mg/dL	18	696	-1.02	<0.0001	-6.78 (0.19) mg/dL
TG	5	259	0.19	0.4331	-4.29 (0.23) mg/dL	16	665	-0.27	0.2403	-0.11 (0.08) mg/dL
ApoB	1	24	ND	ND	ND	2	58	-0.87	0.0065	-0.1 (0.26) g/L
CRP	0	0	ND	ND	ND	4	168	-1.24	0.0284	-1.02 (0.14) mg/L
EAR	1	20	ND	ND	ND	4	117	0.24	<0.0001	0.02 (0.19)
FS	2	44	0.39	0.636	0.34 (0.3) %	4	101	0.50	0.5578	0.83 (0.21) %
LVM	1	24	ND	ND	5 (0.83) g	5	162	-0.06	0.8574	-1.85 (0.19) g
Fasting Insulin	2	189	0.57	0.0618	1.76 (0.17) μIU/mL	10	265	1.53	0.0001	1.53 (0.14) μIU/mL
Fasting Glucose	4	215	0.32	0.2393	0.38 (0.13) mg/dL	11	613	0.78	0.0299	2.12 (0.11) mg/dL
HgbA1c	1	165	ND	ND	ND	6	281	0.65	0.0088	0.09 (0.13) %

ES: effect size; WMD: weighted mean difference; SD: standard deviation.