HDL Cholesterol Subfractions and the Effect of Testosterone Replacement in Hypogonadism

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Introduction

Metabolic problems, such as dyslipidemia, insulin resistance, obesity and diabetes mellitus are common in patients with hypogonadism. Also the cardiovascular morbidity and mortality is significantly increased in these patients. Testosterone replacement well improves sexual dysfunction, muscle strength, osteoporosis and several other clinical aspects of hypogonadism. However, the metabolic and cardiovascular benefits of testosterone regimens are not clearly established. Especially the effects on lipid profiles are complex and not easily understood. The decrements in total and HDL cholesterol concentrations are among the most frequently reported alterations in lipid profiles. However, there is so far no evidence that the decreases in total and HDL cholesterol concentrations cause any alteration in the cardiovascular risk of these patients. Epidemiological reports show a significant inverse relationship between the serum HDL cholesterol concentrations and the number of cardiovascular events. However, nearly half of the cardiovascular events occur in people having normal HDL cholesterol concentrations, implying that the function of HDL cholesterol is more important than its serum levels. HDL cholesterol pool does not consist of homogeneous HDL particles. There are larger, less dense HDL2 and smaller, denser HDL3 subfractions, which interconvert in the arterial wall and plasma. Several reports so far have shown that cardiovascular events are more prevalent in patients with low HDL2 levels, while the role of HDL3 subfractions is not clearly defined. Therefore, we aimed to compare the HDL cholesterol subfractions in an un-confounded group of young and treatment naïve patients with congenital hypogonadotropic hypogonadism (CHH) with those of the healthy subjects. Also we searched for the effects of two different testosterone regimens on the levels of HDL cholesterol and its subfractions.

Material and Methods

70 youngmalepatientswithcongenitalhypogonadotropichypogonadism (CHH) and 70 ageand BMI-matchedhealthymaleswereenrolled in thepresentstudybetween September 2008 and February 2011. The patients were either treated with oil-based injectable blend of four

esterized testosterone compounds (30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate and 100 mg testosterone decanoate) injected for 3 weeks (n=46) or with a daily transdermal administration of testosterone 50 mg gel (n=21). Biochemicalinvestigationsincluding HDL subfractionsandinsulinresistancewere done. The HDL subfractions HDL2 and HDL3 were measured by polyethylene glycol (PEG) precipitation technique. Two different reagents were prepared in different PEG concentrations and pH values as previously described.

Results

The patients with CHH had significantly higher insulin, HOMA-IR ($p<0.001$ for both), WC, triglycerides ($p=0.002$ for both) and diastolic blood pressures ($p=0.04$). There were tendencies towards lower LDL cholesterol, higher fasting glucose and hsCRP levels of the study group. The HDL cholesterol concentrations of the two groups were similar, but there were significant differences between the levels of HDL subfractions. The HDL 2 levels were significantly lower ($p<0.001$) and the HDL3 were significantly higher ($p=0.045$) in patients with CHH (Table-1). The levels of HDL cholesterol and HDL3 subfractions were weakly correlated with the BMI values ($r=-0.198$, $p=0.023$ and $r=-0.233$, $p=0.007$), while there was no other correlation between the remaining study parameters. On the other hand, the HDL2 subfractions were moderately correlated with the levels of insulin ($r=-0.314$, $p<0.001$), HOMA-IR ($r=-0.317$, $p<0.001$), total testosterone ($r=0.333$, $p<0.001$), total cholesterol ($r=0.235$, $p=0.008$), HDL cholesterol ($r=0.211$, $p<0.001$) and LDL cholesterol ($r=0.211$, $p=0.02$). According to the multiple logistic regression analysis, the total testosterone and HDL cholesterol concentrations were the independent determinants of the HDL2 plasma levels (Table-2). No significant side effect was reported during the follow up period in either group. In all the patients, the BMI and WC values significantly increased ($p<0.001$ and $p=0.002$, respectively), while the levels of total cholesterol ($p=0.005$), HDL cholesterol and the HDL 3 ($p<0.001$ for both) significantly decreased. The alterations of the above parameters were not significantly different when the two patient groups treated with different testosterone regimens were compared.

Discussion

The present study shows that young and treatment naïve patients with CHH have unfavorable metabolic profiles when compared with the age and BMI matched healthy counterparts. Namely, the hypogonadal patients have higher WC, DBP, triglyceride, insulin and HOMA-IR measures. The study also shows an unfavorable HDL subfraction composition in these patients. Although the HDL cholesterol concentrations of the two groups look similar, the patients with CHH have significantly lower antiatherosclerotic HDL2 and significantly higher HDL3 subfractions. According to the multiple regression analysis, the low plasma testosterone levels are the significant determinants of the decreased HDL2 subfractions. Whether testosterone replacement improves the cardiometabolic risk in patients with hypogonadism is not clear. Several studies mention favorable effects of testosterone replacement therapy on blood pressures,

dyslipidemia, fasting glucose and insulin levels, while these data are not confirmed in the other reports. Furthermore, a recent study of testosterone replacement was terminated due to the increased cardiac events. According to our results, testosterone replacement therapy increases the WC and the BMI values and significantly decreases total and HDL cholesterol concentrations. However, the decrement of HDL cholesterol concentrations was due to the reduction of HDL3 subfraction, while the anti-atherogenic HDL2 level was not significantly altered. Likewise, high triglycerides, HOMA-IR and hsCRP values were not improved in spite of testosterone replacement therapy. The injectable testosterone regimens are believed to cause higher metabolic side effects due to supraphysiological serum levels. However, this does not seem to be the case in our study, as the metabolic effects were similar between the daily transdermal testosterone gel and thrice weekly testosterone injection groups. Randomized, controlled prospective outcome studies are warranted to identify the cardiometabolic benefits of testosterone replacement therapies.

Table-1: The demographic and biochemical parameters of the patients and the control subjects and the effect of testosterone replacement therapy in the patients.

	Patients (n=70)		**Control Group (n=70)**	**P1**	**P2**
	Before Treatment	**After Treatment**			
Age (years)	22.2±3.1		22.67 ± 2.3	0.291	
BMI (kg/m^2)	22.3 ±3.1	24.1 ± 3.2	22.7 ± 2.4	0.349	**<0.001**
WC (mm)	84.84 ± 10.4	87.35 ± 9.7	79.54 ± 6.9	**0.002**	**0.002**
SBP(mmHG)	117.2 ± 12.1	120.0 ± 11.6	115.2 ±10.9	0.502	0.310
DBP(mmHG)	72.2 ± 8.6	71.8 ± 9.43	68.8 ± 6.0	**0.040**	0.970

Total Chol. (mmol/l)	4.2 ± 0.7	4.0 ± 0.7	4.2 ± 0.71	0.865	**0.005**
LDL Chol. (mmol/l)	2.4± 0.6	2.4 ± 0.6	2.6± 0.6	0.070	0.162
TG (mmol/l)	1.3± 0.8 1.07 (0.9-1.7)	1.4 ± 0.9 1.1 (0.8-1.7)	0.9 ± 0.4 0.9 (0.7-1.1)	**0.002**	0.167
HDL Chol. (mmol/l)	1.2 ± 0.2	1.1 ± 0.2	1.2 ± 0.2	0.945	**<0.001**
HDL2 (mmol/l)	0.2 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	**<0.001**	0.271
HDL3 (mmol/l)	0.9 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	**0.045**	**<0.001**
hs CRP (mg/L)	1.08 ± 1.1 0.57 (0.25-1.51)	1.31 ± 1.97 (0.74 (0.24-1.63)	0.76 ± 0.86 0.52 (0.27-0.82)	0.070	0.299
FBG (mmol/l)	4.8 ± 0.4	4.8 ± 0.5	4.6 ± 0.7	0.060	0.818
Insulin (µU/ml)	9.64 ± 4.2 9.3 (6.1-12.8)	9.80 ± 4.8 8.3 (6.5-12.5)	5.3 ± 3.3 4.8 (3.3-5.8)	**<0.001**	0.840
HOMA-IR	2.05 ± 0.9	2.12 ± 1.04	1.06 ± 0.86	**<0.001**	0.425
Testosterone (nmol/l)	2.7 ± 1.0	7.7 ± 5.0	5.40 ± 1.3	**<0.001**	**<0.001**

Table-2: The logistic regression data having the HDL2 subgroup as the dependent variable.

	Univariate (r,p)		**Multivariate (β,p)**	
T. Testost.	0.333	**<0.001**	0.369	**0.006**
HDL Chol	0.508	**<0.001**	0.271	**0.04**
T. Chol.	0.235	**0.008**	NS	
LDL Chol	0.211	**0.02**	NS	
Insulin	-0.314	**<0.001**	NS	
HOMA-IR	-0.317	**<0.001**	NS	