Dyslipidemia and Superoxide Dismutase Activity in Children with Down Syndrome

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Abstract

Introduction: Down Syndrome (trisomy 21) provides an interesting natural model to study atherosclerosis, since these individuals appear to be protected from plaque formation. **Methodology:** We assessed the lipid levels, and superoxide dismutase (SOD) activity in 32 clinically diagnosed children of Down syndrome and 34 children matched for age and sex as controls. **Results:** SOD activity was found to be significantly higher ($p=0.004$) in children with Down Syndrome (mean=313.7 IU/ml) than in controls (mean140.2 IU/ml). Significantly higher levels of serum triglyceride (154.7 mg/dl) and VLDL (33.9 mg/dl) were observed in Down Syndrome as compared to healthy controls (119.6 mg/dl and 23.9 mg/dl respectively; $p<0.05$ for each). However, the two groups did not show any significant difference in levels of serum HDL-C, LDL-C. **Conclusion:** The raised antioxidant activity of SOD, because of over expression of genes situated non chromosome 21, probably offers some protection against the development of atherosclerosis despite the occurrence of dyslipidemia.

Key words: Chromosome 21, Down Syndrome, Trisomy 21, Superoxide dismutase.

Introduction

Down syndrome (trisomy 21) is the most frequently occurring chromosomal disorder. Studies have proved that advanced maternal age carries the risk of conceiving a baby with this syndrome. At age 20 to 24, it is 1/1490, while at age 40 it is 1/106, and at age 49 is 1/11[1].

Trisomy 21 results in over-expression of genes located on chromosome 21 This chromosome imbalance is the cause of mental retardation, premature aging, and various other disease conditions[2]. The patients with Down syndrome have total number of chromosomes 47, in most cases due to additional chromosome 21, however other chromosomal anomalies have also been found in small number of patients like robertsonian translocation between two 21's with one normal 21 chromosome, translocation of portion of extra chromosome 21 to the long arm of chromosome 21 at region 21q22[3]. Though it's a smallest autosomal chromosome, it bears some important genes like: ribosomal RNA, interferon receptor, cytoplasmic Super Oxide Dismutase (SOD-I), glycineamide phosphoribonucleotide synthetase (GARS), aminoimidazole ribonucleotide synthetase(A'IRS), and liver-type6-phosphofructokinase (PFKL). The interferon receptor gene and SOD-1 have been localized to 21q22, the region that is involved in causing Down syndrome[3]. The presence of additional 21 chromosome imbalances the gene product[4]. SOD1 is an enzyme that in humans is encoded by the *SOD1* gene.SOD1 binds copper and zinc ions and is responsible for destroying free superoxide radicals in the body. It is a soluble cytoplasmic and mitochondrial intermembrane space protein, which acts as a homodimer which convert naturally occurring, but harmful, superoxide radicals to molecular oxygen and hydrogen peroxide[5]. The superoxide dismutases are major defenses against the superoxide anion radical (SODs). Atherosclerosis has been suggested to be linked to the oxidation of lipoproteins, primarily LDL, in the vascular wall[6]. It has been suggested that the

superoxide radical can react with the lipid peroxy radical and alkoxy radical formed during lipid peroxidation and that at least the latter reaction might lead to chain termination and may offer protection from the plaque formation[7].

In Down syndrome patients several metabolic abnormalities have been reported, some involving the lipid metabolism. These patients have high levels of triglycerides, low levels of HDL, down regulation of LDL receptor expression[8]. Fetuses with trisomy 21 have abnormalities of lipid metabolism that are specific and may be genetically determined[9]. Despite the occurrence of hyperlipidemia in patients with down syndrome vascular disease is not as common as in the general population, particularly with respect to the development of atheromas[10].

The patients with Down syndrome appear to be protected from the development of atherosclerosis and the sod levels may have role in protection, so we assessed the lipid levels along with SOD enzyme level.

Materials and Methods

The study was conducted jointly in the tertiary care hospital. The study included clinically diagnosed children of Down syndrome (up to the age of 5 years) and healthy children as controls (age matched to the cases).

Overnight fasting blood samples were collected in plain vials. Serum was used for estimation of lipid profile. Serum total cholesterol and triglyceride were estimated enzymatically. HDL cholesterol was determined by precipitation method. VLDL and LDL were calculated by Friedwalds formula. Hemolysate was prepared from the plasma samples and stored at -20º C till batch analyzed for estimation of SOD activity by the percentage inhibition method. SOD was measured by determining percentage inhibition of the rate of reduction of 2-(4-iodophenyl)-3-(4nitrophenol)-5-phenyltetrazolium chloride to a red formazan dye by superoxide radicals (O2) generated by xanthine and xanthine oxidase.(manual method for superoxide dismutase by RANDOX)

Result obtained were statistically analyzed using SPSS and subjected to student't' test and normal distribution for statistical evalvation.

Results

SOD activity was found to be significantly higher ($p=0.008$) in children with Down syndrome (mean=313.7 IU/ml) than in controls (mean140.2 IU/ml). (Table 1 and Figure 1). Significantly higher levels of serum triglyceride (154.7 mg/dl) and VLDL (31.6 mg/dl) were observed in Down syndrome as compared to healthy controls (119.6 mg/dl and 23.9 mg/dl respectively; $p<0.05$ for each).Though serum LDL-C & total Cholesterol were raised in children of Down syndrome as compared to healthy controls, the difference was not of statistical significance. In the ordinary population this picture leads to atherosclerosis.

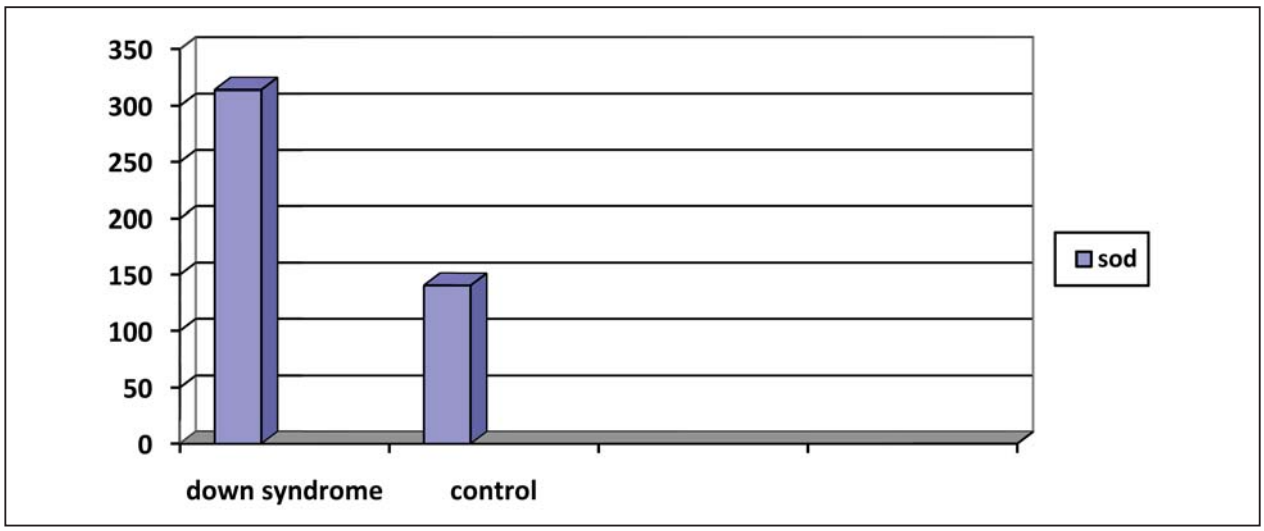

Fig 1: Showing levels of SOD in patients and control

Table 1: Showing SOD and lipid profile of controls and Down syndrome patients

Parameters	Down Syndrome	Controls	*p* value
Superoxide dismutase	313.7IU/ml	140.4 IU/ml	*p*=0.008
Serum Total Cholesterol	154.7mg/dl	142.2 mg/dl	*p*>0.05
Serum Triglyceride	154.7mg/dl	119.6 mg/dl	*p*=0.04
Serum HDL-C	31.6mg/dl	30.6 mg/dl	*p*>0.05
Serum LDL-C	92.8mg/dl	87.6 mg/dl	*p*>0.05
Serum VLDL	31.6mg/dl	23.9 mg/dl	*p*<0.05

Discussion

Down syndrome is a term used to encompass a number of chromosomal anomalies of which trisomy 21 is the most frequent (95% of cases). These patients show an increase of about 50% in SOD-1 activity18-20 (25-27) due to higher levels of SOD-1 protein 21which is the result of extra copy of genetic material in the cell. Other Down syndrome disorders are based on the duplication of the same subset of genes (e.g. various translocations of chromosome 21)[11].

Similar to results reported[12] the SOD levels in blood were significantly higher (p=0.008) in children with Down syndrome (mean=313.7IU/ml) as compared to the control group (mean=140.4IU/ml).

In a study by Salo MK et al[13] plasma total triglyceride concentration was higher in down syndrome patients than in controls. This was reflected in higher VLDL-triglyceride and cholesterol concentrations in these patients. In another study by Dorner K et al[8],down syndrome patients total cholesterol, beta cholesterol, and triglycerides did not differ from the controls, these findings are associated with a higher risk for premature atherosclerosis in general population.

In another study by Zamorano A et al[14] obtained higher values for triglycerides, total cholesterol and LDL cholesterol, with a constant deficit of HDL-cholesterol in all age groups. In the present study also down children show altered lipid profile suggestive of dyslipidimea. A significant increase in serum triglyceride and VLDL levels (p=0.04) was seen in Down syndrome (mean=154.7 mg/dl) compared to healthy controls (mean=119.6 mg/dl) serum cholesterol. LDL levels were also higher in down children than in the control though the difference was not significant. Similarly serum HDL was non-significantly decreased in children with Down syndrome as compared to the control group.

Hypercholesterolemia and atherosclerosis are associated with increased production of reactive oxygen species in the vessel wall, both from vascular cells and macrophages that accumulate within the atherosclerotic lesion[15,16,17]. But mortality causes and pathological findings in Down syndrome show no increased frequency of cardiovascular diseases. Cardiovascular diseases are less common in these patients than in the general population and they have been proposed as "an atheroma free model"[10]. Mortality statistics of these patients showed practically no deaths due to advanced atherosclerosis, and similarly, pathological studies have detected no increase in atherosclerosis – or even a complete absence of atherosclerotic changes. In some cases the arteries of Down syndrome patients had lower percentage of raised lesions and less calcium than the arteries of the control groups[18].

The low incidences of atherosclerosis despite the decreased level of HDL, high levels of TG and VLDL cholesterol leads to the conclusion that The raised anti-oxidant activity of SOD probably offers some protection against the development of atherosclerosis despite the occurrence of dyslipidemia in patients with Down syndrome.

Conclusion

The findings indicate dyslipidemia and increased SOD activity in children with Down syndrome. The raised antioxidant activity of SOD, because of over expression of genes situated on chromosome 21, probably offers some protection against the development of atherosclerosis despite the occurrence of dyslipidemia. The current study may contribute towards a better understanding of the importance of antioxidants in protection against atherosclerosis in hypertriglyceridemias and also the need to re-assess treatment strategies in dyslipidemia.

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