# The Role of Obesity to Inflammatory Factor and Dyslipidemia in Children

## Shelli Faradiana<sup>1</sup>, Aidah Juliaty<sup>2</sup>, Dasril Daud<sup>3</sup>

<sup>1</sup>Senior Resident, Nutrition & Metabolic Diseases Division, Department of Pediatrics, Medical Faculty, Hasanuddin University, Makassar, Indonesia

<sup>2</sup>Supervisor, Nutrition & Metabolic Diseases Division, Department of Pediatrics, Medical Faculty, Hasanuddin University, Makassar, Indonesia

<sup>3</sup>Supervisor & Chief of Department, Hematology & Oncology Division, Department of Pediatrics, Medical Faculty, Hasanuddin University, Makassar, Indonesia

**Abstract:** <u>Introduction</u>: Obesity that occurs in childhood will be a risk factor for cardiovascular disease and metabolic syndrome in adulthood. Inflammation is one of the critical processes associated with the progression of insulin resistance, cardiovascular disease, and obesity is considered as a state of chronic low-grade inflammation. Obesity leads to increased levels in pro-inflammatory cytokines, one of them is TNF-a. <u>Materials and Methods</u>: A cross-sectional study had been conducted from February until March 2015 on Junior High School students (Nusantara's, Islam Athirah's, and Frater's), aged 13-15 years in Makassar who met the criteria for obesity. The samples were divided into two groups: obese group and well-nourish group of children. <u>Results</u>: The numbers of sample that met the criteria were 80 students, consisted of 40 obese students and 40 well-nourish ones. The result of bivariate analyses revealed that TNF-a, triglycerides, LDL, and total cholesterol levels, as well as frequency of dyslipidemia were higher in obese children group compared to the group of well-nourished ones, while HDL level was lower in obese children compared to the group of well-nourished, i.e: TNF-a (p=0.000), total cholesterol (p=0.005), triglycerides (p=0.000), LDL (p=0.000), HDL (p=0.005), and dyslipidemia (p=0.000, OR 16.238 with 95% CI (5.391 to 48.914)). <u>Conclusion</u>: The high level of TNF- a, total cholesterol, triglycerides, LDL, low level of HDL, and high frequency of dyslipidemia were more common in obese children than in a group of well-nourished.

Keywords: TNF-a, Lipid profile, Obese children

#### 1. Introduction

Obesity is associated with significant health problems in children and predispose to obesity in adulthood, as well as the onset of metabolic and cardiovascular co morbidities and mortality.<sup>[1, 2]</sup> At the national level, the prevalence of obese children aged 13-15 years was 2.5% in 2010.<sup>[3]</sup> An increase in the prevalence of obese adolescents aged 13-15 years in the year 2013 up to 10.8%.<sup>[4]</sup> The associated etiology with obesity in children is multifactorial. Genetic and environmental factors play an equally important role as a causative factor.<sup>[5]</sup>

According to the laws of thermodynamics, obesity occurs because of an imbalance between energy intakes with the energy use (energy expenditures) so that there is excess energy that is stored in the form of fatty tissue. Research conducted by Mandal et al. identify the consumption of fast food, sedentary lifestyle, high socio-economic status, alcohol consumption, and are within the nuclear family as a risk factor for obesity in adolescents.<sup>[1, 6]</sup>

Adipose tissue in obesity showed inflation and progressive infiltration of macrophages in line with the development of obesity. The size changes of adipocytes and fat pads lead to physical changes and paracrine functions of adipocytes. On obesity, the adipocytes cells secrete TNF- $\alpha$  levels were low, which can stimulate pre-adipocytes to produce MCP-1 (monocyte chemo attractant protein-1). In addition to adipocytes cells, endothelial cells also secrete MCP-1 in response to cytokines. MCP-1 is used to summon macrophages into the tissue adipocytes. Macrophages, together with adipocytes cells can produce pro-inflammatory cytokines (TNF- $\alpha$ ) and Fatty Acid-Binding Protein (FABP) continuously. The increased production of these factors will re-activate macrophages, causing a feedback mechanism that causes a decrease in adipocyte function that can lead to fat accumulation in adipocytes and cholesterol in macrophages which can result in insulin resistance and atherosclerosis.<sup>[7]</sup>

Adipokines or adipositokin are cytokines (proteins which function in the exchange process of information from cell to cell) that is secreted by adipocytes network, among others, is TNF- $\alpha$ , plasminogen activator inhibitor-1 (PAI-1), IL6, leptin, resistin and angiotensinogen, whose levels are increased in obesity, while adiponectin, the levels are decreased in obese.<sup>[8]</sup>

Many studies have shown a correlation between high serum lipid levels with the incidence of coronary heart disease and atherosclerosis in humans.<sup>[9-12]</sup> Research conducted by Juonola et al. which involved 2265 children aged 3-18 years shows that dyslipidemia have a damaging effect on the blood vessels that have been initiated since childhood.<sup>[13]</sup> Children with dyslipidemia are more prone to risk of cardiovascular disease and metabolic syndrome.

Various studies have been carried out to look at the relationship between inflammatory factors and dyslipidemia as a risk factor for cardiovascular disorders in obese adolescents. Research conducted by Sinaiko et al. which involved 295 obese and not obese adolescents with a mean age of 15 years, showed the triglycerides increased significantly, whereas the HDL cholesterol levels are

decreased in obese adolescents (p = 0.002).<sup>[14]</sup> In Indonesia, the study by Himah et al. on 53 obese and well nutrition children, shows that obese children have a greater risk for elevated the triglyceride levels (RR 2.6; p <0.001) and decreased levels of HDL cholesterol (RR 17, 8; p = 0.003) and the risk for the occurrence of dyslipidemia in obese children is 5.2 times higher compared to non-obese children (p = 0.002).<sup>[15]</sup>

The purpose of this study was to analyze the role of obesity on inflammatory factors (TNF- $\alpha$ ) and dyslipidemia in obese and well nutrition children.

## 2. Materials and Methods

This study used a cross-sectional design to measure the levels of TNF- $\alpha$  and lipid profile (triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol), and compared the levels of TNF- $\alpha$ , lipid profile, and the frequency of dyslipidemia among obese and well nutrition children. We obtained a sample of 80 children, which is 40 (50%) obese children and 40 (50%) of the well nutrition children by conducted a comparative analyses of the levels of TNF- $\alpha$  and levels of lipid profiles in obese and well nutrition children.

This research was conducted in the Junior High Schools of Nusantara's, Athirah's, and Frater's in Makassar from February to March 2015. This study population is the eligible students of junior high school aged 13-15 years in Makassar, which comes from private schools with status of middle and upper socio-economic, to obtain a high probability of obesity, with the possibility to obtain a greater prevalence of dyslipidemia compared with younger children. We then measured the weight and height, and then calculated the body mass index to determine obesity. The control subjects were taken from children with well nutritional status after giving the informed consent. All the eligible patients were noted: name, age, sex, weight, height, and BMI. Weight measurement is using digital bathroom scales that have been calibrated to the nearest 0.1 kg. Height measurement using microtoise to the nearest 0.1 cm. Nutritional status is determined based on body weight for height according to NCHS standards. Then calculate BMI for patients who have been grouped in the nutritional status of obese, which is obtained from the measurement of body weight (kg) divided by the square of height (meters) = (kg/ m2). The recording of sample data is followed by examination of TNF- $\alpha$  levels, and blood lipid profiles. The data obtained are grouped by its type of data into the groups of obese and well nutrition, and then each was analyzed in accordance with appropriate statistical methods, the analyses of univariate and bivariate.

## 3. Results

Table 1 shows the characteristics of study were assessed in the form of sex, age, weight, height, and BMI. For the category of sex, in the group of obese children consisted of 27 male (67.50%) and 13 female students (32.50%), whereas in the group of well-nourished children consisted of 24 male (60.00 %) and 16 female students (40.00%) (p = 0.485). The age group of obese children obtained a median of 13.7 years, and 13.88 for well nutrition children (p = 0.414). The mean weight of obese children group 75.47 with a standard deviation of 11.694, while in the group of well-nourished of 52.92 with a standard deviation of 4.503 (p = 0.000). The mean height is 1.58 of obese children with a standard deviation of 0.072, while in the group of well nourished is 1.58 with a standard deviation of 0.065 (p = 0.821). BMI Median of obese and well nutrition children, respectively for 29.56 and 21.14 (p = 0.000).

NT		Body N		
NO.	Sample characteristics	Obese (N=40)         Well nourished (N=40)		р
1.	Sex*			
	Male (%)	27 (67.50)	24 (60.00)	0.485
	Female (%)	13 (32.50)	16 (40.00)	
2.	Age (years)***			
	Mean	13.77	13.88	
	Median	13.75	13.80	0.414
3.	Standard Deviation	0.475	0.485	
	Average	13.10 - 14.90	13.10 - 15.00	
	Weight (kg)**			
	Mean	75.47	52.92	
	Median	72.80	52.05	
4.	Standard Deviation	11.694	4.503	0.000
	Average	56.00 - 100.60	45.00 - 64.00	
	Height (m)**			
5.	Mean	1.58	1.58	
	Median	11.58	1.58	
	Standard Deviation	0.072	0.065	0.821
	Average	1.43 - 1.74	1.45 - 1.76	
	Body mass index (kg/m <sup>2</sup> )***			
	Mean	30.24	21.23	
	Median	29.56	21.14	0.000
	Standard Deviation	3.002	1.601	
	Average	26.26 - 39.54	17.11 - 24.56	

Table 1: Study characteristics

\*Chi Square \*\*t-test \*\*\*Mann Whitney

Table 2 shows in the group of obese children, the median levels of TNF- $\alpha$  are 33.743; whereas in the group of well-nourished children obtained median levels of TNF- $\alpha$  at 3.540. Statistical analyses showed levels of TNF- $\alpha$  in obese children is higher than the levels of TNF- $\alpha$  on the well nourished children with a value of p = 0.000 (p <0.05).

 Table 2: Comparison of TNF-α levels among obese and well nutrition children

	$TNE \approx (n \approx m)$	Nutritional status			
	ΠΝΓ-α (pg/nn)	Obese	Well nourished		
	Mean	32.061	4.526		
	Median	33.743	3.540		
	Standard Deviation	11.254	2.519		
	Min-Max	10.76 - 55.47	1.74 - 10.67		
Mann Whitney test		p = 0.000 (	(p < 0.05)		

In Table 3, it can be seen that in the group of obese children, the average HDL cholesterol levels at 46.950 with a standard deviation of 8.111, while in the group of well-nourished children, the average HDL cholesterol levels at 53.425 with a standard deviation of 11.455. Statistical analyses showed HDL cholesterol levels in obese children is lower than the HDL cholesterol levels in children with well nutritional value of p = 0.005 (p < 0.05).

In the group of obese children, the median LDL cholesterol level of 142.500; whereas in the group of well-nourished children, the median LDL cholesterol levels at 109.500. Results of statistical analyses in Table 3 shows that LDL cholesterol levels in obese children is higher than the levels of LDL cholesterol in children with well nutritional value of p = 0.000 (p <0.05).

In the group of obese children, the average total cholesterol by 183.500 with a standard deviation of 33.334, while in the group of well-nourished children, the average total cholesterol by 164.650 with a standard deviation of 23.957. Results of statistical analyses in Table 3 shows that total cholesterol levels in obese children is higher than the total cholesterol levels in children with good nutritional value of p = 0.005 (p <0.05).

From Table 3 shows that in the group of obese children, median triglyceride levels by 116.500; whereas in the group of well-nourished children, the median triglyceride level at 78.500. Statistical analyses showed levels of triglycerides in obese children is higher than the levels of triglycerides in children with well nutrition with p = 0.000 (p <0.05).

N		Nutrition		
NO.	Dyslipidemia	Obese	Well nourished	р
		(N=40)	(N=40)	
1.	HDL (mg/dl)* Mean	46 950	53 125	
	Median	46,000	52 000	0.005
	Standard Deviation	8 111	11 455	0.005
	Min-Max	34.00 - 64.00	31.00 - 80.00	
•		5 1.00 0 1.00	51.00 00.00	
2.	LDL (mg/dl)** Mean	142.900	105.225	
	Median	142.500	109.500	0.000
	Standard Deviation	23.492	20.589	
	Min-Max	100.00 - 184.00	66.00 - 136.00	
3.	Cholesterol Total (mg/dl)*			
	Mean	183.500	164.650	
	Median	180.000	166.00	0.005
	Standard Deviation	33.334	23.957	
	Min-Max	112.00 - 248.00	124.00 - 233.00	
4.	Triglyceride (mg/dl)**			
	Mean	122.950	89.950	
	Median	116.500	78.500	0.000
	Standard Deviation	43.967	34.081	
	Min-Max	49.00 - 264.00	44.00 - 179.00	

**Table 3:** The comparison of dyslipidemia among obese and well nutrition children

\*t test \*\*Mann Whitney test

Table 4 shows the group of obese children, dyslipidemia occurs at 82.5% (33 students), whereas in the group of well-nourished children, occurs dyslipidemia at 25% (10 students). Results of statistical analyses in Table 4 shows that there is a relationship between dyslipidemia group with

nutritional status, with a value of p = 0.000 (p < 0.05). Value odds ratio (OR) = 14.143 with 95% CI (4.779 to 41.858), which means that the risk of occurrence of dyslipidemia in obese children amounted to 14.143 times as compared to well-nourished children.

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Tuble 4. Dyshpideinia felationship with hautional status						
Dualinidamia	Nutritional status		OB	CL 059/		
Dystipideititä	Obese	Well nourished	OK	CI 95%		
Yes	33 (82.5%)	10 (25%)	14 142	4 770 41 959		
No	7 (17.5%)	30 (75%)	14.145	4.//9-41.636		
Total	40 (100%)	40 (100%)				

Table 4: D	) yslipidemia	relationship	with	nuti	ritional	status

Chi Square test

 $p = 0.000 \ (p < 0.05)$ 

Table 5: Characteristics of dyslipidemia based on nutritional status

Linid mofile	Obese		Well nourished	
Lipid profile	Amount	%	Amount	%
cHDL	2	5	3	7.5
cLDL	9	22.5	2	5
Cholesterol	0	0	0	0
TG	2	5	1	2.5
cHDL+cLDL	2	5	0	0
cHDL+ Cholesterol	0	0	0	0
cHDL+TG	0	0	1	2.5
cLDL+Cholesterol	7	17.5	1	2.5
cLDL+TG	4	10	0	0
Cholesterol +TG	0	0	1	2.5
cHDL+cLDL+ Cholesterol	1	2.5	1	2.5
cHDL+cLDL+TG	2	5	0	0
cHDL+Cholesterol +TG	0	0	0	0
cLDL+Cholesterol +TG	3	7.5	0	0
cHDL+cLDL+ Cholesterol +TG	1	2.5	0	0
Total	33	82.5	10	25

In obese children group (40 children), there were 33 (82.5%) children who have dyslipidemia. From the group of disturbed lipid profile in dyslipidemia, which obtained the highest frequency of 9 (22.5%) children with abnormal levels of LDL cholesterol. While the lowest frequency, was found in 1 (2.5%) children with four abnormal lipid profiles (HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides).

In the group of well-nourished children (40 children), there were 10 (25%) of children who have dyslipidemia. From the group of disturbed lipid profile in dyslipidemia, which obtained the highest frequency of 3 (7.5%) children with abnormal HDL cholesterol levels. While the lowest frequency, was found in 1 (2.5%) of children with three disorder of lipid profile (HDL cholesterol, LDL cholesterol, total cholesterol).

## 4. Discussion

This study shows the role of obesity on inflammatory factors (TNF- $\alpha$ ) and dyslipidemia in obese and well nutrition children. This study was done because obesity in children associated with various cardiovascular diseases and metabolic diseases as adults, it is according to research conducted by Subardia et al. that obesity is a significant health problem in children and predispose to obesity in adulthood, as well as the onset of metabolic and cardiovascular co morbidities and mortality.<sup>[2]</sup>

An important new development in the understanding of obesity is a concept that marked obesity as a chronic lowlevel inflammation.<sup>[16]</sup> This state is indicated by the presence of elevated levels of several pro-inflammatory cytokines in the blood circulation one of which is TNF- $\alpha$ . The increased inflammation due to TNF-a causes increased insulin resistance and other disorders associated with obesity, such as dyslipidemia and metabolic syndrome. The presumption of inflammation as a consequence of obesity, showing that obesity is proven as an inflammatory disease.<sup>[8]</sup>

In this study we found no statistically significant differences in the sex ratio of male and female on the nutritional status with a value of p = 0.485 (p> 0.05), which means that sex did not affect the nutritional status. This means that sex does not give a bias in the analyses of dyslipidemia among groups of obese and well nutrition children. This is in line with the research by Hariyanto et al. which the 64 teenagers who studied the factors that influence obesity in adolescents, reported that there was no effect of sex on the nutritional status (p = 0.54).<sup>[17]</sup>

Statistical analyses comparing the levels of TNF- $\alpha$  between obese and well nutrition children indicate that there are significant differences in the levels of TNF- $\alpha$  between the two groups of children, where the levels of TNF- $\alpha$  in obese children is higher than the levels of TNF- $\alpha$  on the well nutrition children with a value of p = 0.000 (p < 0.05). Juliaty and Breslin et al. reported that TNF- $\alpha$  levels were significantly greater in obese children compared to wellnourished children (p <0.05).<sup>[18, 19]</sup>

On average HDL cholesterol levels in obese children is lower than in well nutrition children. Statistical analyses shows that there are significant differences between the HDL cholesterol levels of obese children and children with good nutritional value of p = 0.005 (p < 0.05). This is in line with the studies conducted by Bennett et al. which examined 123 pre pubertal children (7-9 years) showed that HDL cholesterol levels in the group of obese children is lower than the not obese children group (p <0.01) and after being adjusted obtained value p = 0.04.<sup>[20]</sup> The results of this study were supported, but the age of the studied subjects was younger. This suggests that high cholesterol levels have been found in children with younger age, so the risk to develop complications of obesity may occur earlier. Haryanto et al. also found that the HDL cholesterol levels in the group of obese children is lower compared to wellnourished children group (p = 0.004).<sup>[17]</sup>

Statistical analyses of the results of the comparison between the LDL cholesterol levels of obese and well nutrition children indicate that there are significant differences in LDL cholesterol levels in both groups of children, where the levels of LDL cholesterol in obese children is higher than the levels of LDL cholesterol in children with well nutritional value of p = 0.000 (p < 0.05). These results are consistent with the research conducted by Simsek et al. who reported that LDL cholesterol levels in obese children is higher than the levels of LDL cholesterol in not obese children, with p <0.001.<sup>[11]</sup> Research by Hariyanto et al. also found that higher levels of LDL cholesterol in the group of obese children compared with children of normal weight, where the average LDL cholesterol levels in the group of obese children at 112.6 with a standard deviation of 31.0 and in the group of children with normal weight average LDL

cholesterol level of 82.9 with a standard deviation of 21.7 (p = 0.001).<sup>[17]</sup>

The results of comparative analyses of total cholesterol levels between obese and well nutrition children showed that the average total cholesterol levels in obese children is higher than in well-nourished children. This is supported by the results of the statistical analyses that shows there are significant differences in total cholesterol levels in both groups of children, with a value of p = 0.005 (p < 0.05). Research by Mexitalia et al. shows the same thing, where the average total cholesterol levels in the group of obese children at 183.0; whereas in the group of not obese children mean total cholesterol level of 157.3 (p < 0.001).<sup>[21]</sup> Kim et al. also reported that total cholesterol levels in the group of obese children is higher than the well-nourished children group (p < 0.0001).<sup>[22]</sup>

Statistical analyses comparing triglyceride levels between obese and well nutrition children indicate that there are significant differences in triglyceride levels in both groups of children, where the levels of triglycerides in obese children is higher than the levels of triglycerides in well nutrition children with a value of p = 0.000 (p < 0.05). These results are supported by research conducted by Simsek et al. which showed that triglyceride levels in obese children is higher than the levels of triglycerides in not obese children, with p < 0.001.<sup>[11]</sup> Research conducted by Himah et al. showed that the group of obese children had higher levels of triglycerides were 2.6 times higher than the group of not obese children.<sup>[15]</sup> The study by Kim et al. also reported that triglyceride levels 2.8 times higher in obese children compared with groups of not obese children.<sup>[22]</sup>

The frequency of children who have dyslipidemia found more in the group of obese children is 33 people (82.5%) compared with the group of well nourished children as many as 10 students (25%). Statistical analyses showed that there were significant differences between the groups of obese with well nutrition children on the incidence of dyslipidemia, with a value of p = 0.000 (p <0.05). OR = 14.143 values with 95% CI (4,779- 41.858), this means that the risk of obese children to experience the dyslipidemia is 14.143 times compared to well-nourished children. In this study, obese children who had dyslipidemia not only because of changes in one of the existing lipid profiles, but there are more than one and even a change of the entire lipid profile which there is a high total cholesterol, high triglycerides, high LDL cholesterol and low HDL cholesterol can increase the risk of cardiovascular disease events.

Research by Gergerenchi in obese children and adolescents aged 4-18 years in Iran reported the prevalence of dyslipidemia in obese children by 69.58% compared with the not obese child, with p <0.004 ( $p \le 0.05$ ).<sup>[23]</sup> Research by Casavalle, et al. in Argentina on 139 children aged 8-14 years were overweight and obese showed that the prevalence of dyslipidemia of 50.4%.<sup>[24]</sup> Research by Himah, et al. showed that the group of obese children has a risk of dyslipidemia 5 times higher than the group of not obese children. This indicates overweight and obese children are

easier to experience dyslipidemia and metabolic syndrome.  $^{\left[ 15\right] }$ 

Additionally, in children, there are various factors cannot be avoided that could affect the lipid profile and levels of TNF- $\alpha$  in addition to obesity, such as genetic factors, metabolic disorders, endocrine, diet, drugs, smoking, physical activity, parasitic infestations, nephritic syndrome, and infection. These factors are not examined in this study. It is also a disadvantage in this study. According to Pereira there is an increase in the percentage of 10-year risk for cardiovascular disease and metabolic syndrome in obese children who have one risk factor changes in lipid profiles than obese children who had  $\geq 2$  risk factors.<sup>[25]</sup> Among the lipid profile variables and dyslipidemia were analyzed against the group of obese and well nutrition children, it appears that the frequency of occurrence of high total cholesterol, high triglycerides, high LDL cholesterol, and dyslipidemia, differ significantly in obese children compared with well nutrition children.

Dyslipidemia is a lipid profile levels in the abnormal blood. Dyslipidemia abnormalities are at least one blood lipid profile. In the group of obese children who had dyslipidemia, the highest frequency of occurrence of dyslipidemia was found in 9 (22.5%) children with only one abnormal lipid profile, namely LDL cholesterol, and the least was found in 1 (2.5%) of children with abnormalities fourth lipid profile (HDL cholesterol, LDL cholesterol, TG, and cholesterol). Meanwhile, in the group of well nutrition children who had dyslipidemia, the highest frequency of occurrence of dyslipidemia was found in 3 (7.5%) children with only one abnormal lipid profile, namely HDL cholesterol, and the least was found in 1 (2.5%) of children with three abnormalities of lipid profile (HDL cholesterol, LDL cholesterol, and total cholesterol). It can be shown that in obese children, lipid profile disorders are more prevalent than in well-nourished children. Both in obese and well nutrition children, lipid profile abnormalities have occurred early on. Besides, both in obese and well nutrition children, the beginning of the lipid profile abnormalities are not the same in every sample, which may explain why obese children there is a subject that is not abnormal lipid profile, there are experienced only one aberration profile lipids, and some are experiencing abnormalities two lipid profile, and some even have abnormalities in the fourth lipid profile, as well as with child nutrition, there is a subject that is not abnormal lipid profile, and some even have abnormalities in 1 to 3 lipid profile. Various characteristics of both lipid profile abnormalities in obese children as well as on well nutrition occurs because taking lipid profile is only done once simultaneously, so that it is the primary weakness in this study. Various characteristics of a good lipid profile picture on obese and in well nutrition children are shown in Table 5, show that these characteristics could be a temporary phenomenon or abnormal lipid profile can be continued.

In contrast to other diseases which can usually be easily recognizable symptoms, not the case with people who have changes in lipid profile? The absence of typical symptoms as a result of dyslipidemia in children, making children with changes in lipid profile is recommended to carry out checks total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol regularly, because persistence of abnormal lipid profile can cause morbidity and mortality in later life.

## 5. Conclusion

Based on the results of the study concluded that the levels of TNF- $\alpha$ , total cholesterol, triglycerides, and LDL in the group of obese children is higher than the group of well nutrition children; whereas the HDL cholesterol levels in the group of obese children is lower than the group of well nutrition children.

## 6. Future Scope

It is necessary to conduct further research on the role of the TNF- $\alpha$  obesity and dyslipidemia using multicenter prospective cohort study design to control the other factors that affect the incidence of obesity. Such factors like race, genetic, pubertal status, and diet. This study can also be used as input to the unit while education in developing strategies in schools for the prevention and management of disorders of lipid profile in children as early intervention on the risk of cardiovascular disease later in life, by the dietary adjustments, increased physical activity, and sports.

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