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Original Research Article

Correlation of HDL cholesterol serum and Wagner's severity level of diabetic foot ulcers

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ABSTRACT

Background: Diabetic foot ulcers are one of the leading causes of amputation in non-traumatic patients. This research aimed to investigate the correlation between the level of HDL cholesterol and the severity level of diabetic foot ulcer based on Wagner classification. The study conducted at Wahidin Sudirohusodo Hospital, Makassar, Indonesia.
Methods: This is an observational study with the cross-sectional design. The data collected before and after the treatment. The change of the levels of HDL cholesterol and the severity level of the diabetic foot ulcer based on Wagner classification during the treatment were analyzed. Data analyzed using Spearman Correlation test, the paired t-test to assess the change in the levels of HDL cholesterol and the levels of severity of diabetic foot ulcer based on Wagner classification at the time admission and after the treatment. ANOVA test was used to observe the reduction significance of the severity of diabetic foot ulcer based on Wagner classification, and it was categorized as significant if $p<0.05$.
Results: The results indicated that there is a correlation between the level of HDL cholesterol and the severity level of diabetic foot ulcer based on Wagner classification either at the early treatment with p-value = 0.003 (r = - 0.448) and the end of the treatment with p-value = 0.001(r = - 0.477). The lower of the level of cholesterol HDL, the higher was the severity level of the diabetic foot ulcer. Meanwhile, the correlation between the increase of the level of HDL cholesterol and the reduction of Wagner classification during the treatment was statistically insignificant with p-value = 0.100 (r = - 0.215).
Conclusions: there was a correlation between elevated HDL cholesterol levels during treatment with Wagner classification decrease during treatment, the higher the HDL change, the higher the Wagner classification, but this was weak correlation and statistically insignificant.

Keywords: HDL cholesterol, Ulcers, Wagner classification

INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases in nearly all countries, and its prevalence is on the increase as changing lifestyles lead to reduce physical activity and increased obesity.[1,2] Diabetes mellitus is a chronic metabolic disease with micro and macrovascular complications.[3] The global prevalence rate is around 5-6%, the International Diabetes Federation (IDF) estimates the number of DM patients worldwide is 285 million, and

by 2030 that number is expected to be 438 million.[4] WHO reports that more than 347 million people worldwide suffer from diabetes mellitus.[5] The increased prevalence of DM accompanied by longer life expectancy results in complications in chronic diabetes also increased.[4]

Patients with diabetes mellitus are twice as likely to have foot problems and peripheral arterial disease (PAD) in lower extremities than those without DM.[4] Diabetic foot is a major long-term complication occurring in DM patients and associated with increased morbidity and mortality rates in these patients.[6] Approximately 15-25% of patients with diabetes mellitus will develop into diabetic foot during their lifetime.[7]

Diabetic foot ulcers are a major cause of amputation in non-traumatic patients, about 85% of amputations in diabetic foot ulcers are due to extensive infection or gangrene.[4,8] Amputation of the lower limb is one of the most feared complications in DM patients because it affects the health and quality of life of the patient.[7] The risk of amputation increased in diabetic patients with peripheral neuropathy, where peripheral neuropathy leads to loss of sensation and ability to detect problems occurring in the legs causing changes that may increase pressure on the feet resulting in ulcers.[9]

The treatment required for current diabetic foot ulcers is by providing optimal blood supply, handling at pressures on the sole, preventing and controlling the right infection.[10,11] However, mechanisms and estimates for increased risk of amputation in patients with diabetic foot ulcers are difficult to understand, and diabetic foot ulcers are still difficult to manage.[7]

A previous study by Ikura et al showed a correlation of low HDL cholesterol levels with severity in diabetic foot ulcers with an increased incidence of infection, and they also evaluated the hypothesis that HDL cholesterol was a predictor of amputation and injury in patients with ulcers diabetic foot.[7] High-Density Lipoprotein (HDL) has a role in reverse cholesterol transport (RCT), but it also has a direct role that affects cardiovascular and another metabolism.[12] In endothelial cells, HDL decreases apoptosis, stimulates endothelial cell proliferation and migration, anti-inflammatory and antithrombotic effects.[13,14] HDL work also stimulates pancreatic β cells to secrete insulin, protects pancreatic β cells from apoptosis and also increases glucose uptake by muscle cells.[15] HDL also has a crucial role in host defense systems as the innate immune system and HDL association with the pathogenesis of acute responses to infection and sepsis.[16]

Based on the above description, we are interested in investigating the correlation between serum HDL cholesterol level with the severity of diabetic foot ulcers based on Wagner's classification in Wahidin Sudirohusodo Hospital Makassar. Because diabetic foot ulcer case is quite large in Makassar, research on the correlation between serum HDL cholesterol level with the severity of diabetic foot ulcers has never been done in Indonesia and Makassar in particular, and serum HDL cholesterol testing is relatively easy to do.

METHODS

This study uses an observational research design with a cross-sectional design. The study variables consist of: free variable (HDL cholesterol level In DM patient), intermediate variable (atherosclerosis, ischemia), dependent variable (diabetic foot ulcer), and moderator variable (age, smoking, hypertension, obesity).

The study was conducted at Dr. Hospital. Wahidin Sudirohusodo in Makassar. Study time from October 2016 to May 2017. The sample of the study was in-patient and outpatient diabetic foot ulcers who met the inclusion criteria, and 37 samples were obtained.

Interviews and anamnesis were performed in patients suffering diabetic foot ulcers and then conducted physical examinations of patients including blood pressure, height, and weight. Determine the diabetic foot diabetic foot ulcers based on the Wagner classification. Doing laboratory test of Fasting Blood Sugar, 2 Hour Blood Sugar PP, HbA1c, and HDL cholesterol. Determine the grading of patient diabetic foot ulcers based on Wagner's classification when the patient will return for treatment or during control in the polyclinic. Conduct laboratory examination of HDL cholesterol when the patient is going home from treatment or during monitoring in the polyclinic. The data that have been collected and then analyzed statistically then reported in the form of research results.

Statistical analysis

Data analyzed using SPSS version 22 and statistic method used was statistical value calculation with Spearman Correlation Test, Paired T-test, and ANOVA test and stated significant when $p < 0,05$

RESULTS

Observational research has been done with cross-sectional design to know the correlation of HDL cholesterol level with the severity of diabetic foot ulcers based on Wagner classification in Wahidin Sudirohusodo Hospital Makassar. During this period, there were 37 subjects who met the criteria of the study sample, consisting of 24 men (64.9%) and 13 women (35.1%). According to the age group, the majority of people over the age of 60 were 17 people (45.9%), then age 50-59 years were 13 persons (35.2%) and aged 40-49 years were 7 (18.9 %). Based on the classification of Wagner at admission (early) it appears that no (0%) diabetic foot ulcers in Wagner 0.

Table 1: Characteristics of subject.

Variable	N	%
Sex		
Men	24	64.9
Women	13	35.1
Age		
40-49 years	7	18.9
50-59 years	13	35.2
>60 years	17	45.9
Wagner classification (early)		
0	0	0
1	3	8.1
2	4	10.8
3	9	24.3
4	16	43.2
5	5	13.5
Wagner classification (end)		
0	5	13.5
1	14	37.8
2	11	29.7
3	7	18.9
4	0	0
5	0	0

Most patients found in Wagner 4, 16 people (43.2%), then Wagner 3 as many as 9 people (24.3%), Wagner 5 as many as 5 people (13.5%), Wagner 2 as many as 4 people (10.8%) and Wagner 1 as many as 3 people (8.1%). After treatment or control in polyclinics (end) it appears that no diabetic foot ulcer sufferers (0%) were present in Wagner 4 and 5, Wagner 1 was 14 (37.8%), and Wagner 2 as many as 11 people (29.7%), Wagner 3 as many as 7 people (18.9%), and Wagner 0 as many as 5 people (13.5%) (Table 1).

HDL cholesterol levels in each Wagner Classification indicated that before treatment (early), in the Wagner 1 classification the mean HDL cholesterol level was 47.66 mg/dl, the HDL level in Wagner 2 averaged 34.25 mg/dl, HDL levels in Wagner 3 averaged 30 mg/dl, HDL levels in Wagner 4 averaged 27.56 mg/dl, and Wagner 5 averaged 19.4 mg/dl. After treatment or control at the polyclinic (end) was seen in the Wagner classification of 0 HDL cholesterol levels averaged 58 mg/dl, HDL levels in Wagner 1 averaged 41.6 mg/dl, HDL levels in Wagner 2 averaged 34, 4 mg/dl, and at Wagner 3 the mean HDL level was 33.3%. This shows that the higher the Wagner classification, the lower the HDL cholesterol (Table 2).

Table 2: HDL cholesterol levels on each Wagner classification.

Variable	Wagner Classification					
	0	**1**	**2**	**3**	**4**	**5**
HDL Level (early) (mg/dl)	0 (n=0)	47.66 (n=3)	34.25 (n=4)	30 (n=9)	27.56 (n=16)	19.4 (n=5)
HDL Level (end) (mg/dl)	58 (n=5)	41.6 (n=14)	34.4 (n=11)	33.3 (n=7)	0 (n=0)	0 (n=0)

Changes in HDL cholesterol and severity of diabetic foot ulcers based on Wagner's Classification showed that HDL cholesterol levels before treatment (early) with a mean (SD)=29.41 (9.77) mg/dl and after treatment (end) HDL level mean (SD)=40, 11 (10.3) mg/dl, average mean change of HDL level of 10.7 mg/dl and p-value <0.001. Wagner's pre-treatment classification had an average grade of 3.43 (SD 1.12), and after the average treatment classification of Wagner 1.38 (SD 0.79), there was a change of 2.05 with a p-value <0.001 (Table 3).

Table 3: Changes in HDL cholesterol levels and severity of diabetic foot ulcer based on Wagner classification.

Variable	Early	End	Average change	p*
	$\overline{X}$ ±SD	$\overline{X}$ ±SD		
HDL	29.41±9.77	40.11±10.3	10.7	<0.001
Wagner	3.43±1.12	1.38±0.79	2.05	<0.001

The correlation of HDL cholesterol with severity of diabetic foot ulcers based on Wagner classification by Spearman correlation test showed HDL correlation with diabetic foot ulcer level based on Wagner classification before treatment (early) p value = 0.003 (r = -0.448), after treatment (end) value of p = 0,001 (r = -0,477) and on correlation of HDL level change with Wagner classification was obtained p=0.100 (r =-0.215) (Table 4).

Table 4: Correlation of HDL cholesterol levels with severity of diabetic foot ulcer based on Wagner classification.

Variable	r	p*
HDL with Wagner (early)	-0.448	0.003
HDL with Wagner (end)	-0.477	0.001
HDL changes with Wagner changes	-0.215	0.100

*Spearman Correlation test

Increased serum HDL cholesterol levels based on the magnitude of Wagner classification decrease during treatment showed a significant increase in HDL cholesterol levels by the extent of reduced severity of diabetic foot ulcers based on Wagner classification. The decrease in HDL cholesterol level was 9.7 (SD 4.1) mg/dl, at the 2nd grade level of Wagner decrease, there was an increase of HDL cholesterol level by an average

of 10.3 (SD 3.8) mg/dl, a reduction in the grade 3 Wagner classification was found to increase HDL cholesterol levels by an average of 12.2 (SD 6.9) mg/dl. But it is not statistically significant where the value p = 0.487 (Table 5).

Table 5: Increased HDL serum cholesterol levels based on Wagner classification of Wagner decrease during treatment.

Decreased Wagner classification	Increased HDL level $\overline{X}$ ±SD	p*
1 Level	9.7±4.1	
2 Level	10.3±3.8	0.487
3 Level	12.2±6.9	

DISCUSSION

This study shows that there is a correlation between HDL cholesterol levels with diabetic foot ulcer severity based on Wagner's classification, either at the start of treatment or after treatment. The lower the HDL cholesterol level, the higher the severity of diabetic foot ulcers. There was a correlation between elevated HDL cholesterol levels during treatment with a decrease in Wagner's classification during treatment, but this correlation was weak and statistically significant.

Description of age with age 40 years old and most aged 69 years old with average score 56,36 (SD 8,05) year. This is by research conducted by Zubair et al. (2015), which states that in developing countries, the majority of DM patients are at the age of 45 to 64 years.[1] Manda et al's study, also stated that the mean age studied was 54.7 + 10.2 years, while the study of Ikura et al, age studied had an average value of 62 (SD 14) years. This suggests that the occurrence of diabetic foot ulcers occurs in the fifth and sixth decades.[7,9]

The age group with the most diabetic foot ulcers was age over 60 years (45.9%) followed by age 50-59 years (35.2%) and the lowest at 40-49 years old (18.9%), this is also explained by Zubair et al (2015), that the prevalence of diabetic foot ulcers increases with age over 40 years.[1] In a study conducted by Manda et al, there was also a distribution of diabetic foot ulcers found in more than 75 percent aged 30 to 60 years, and the highest number at age 50-59 years (42.5%).[9]

Description of the minimum value of GDP, GD2JPP and HbA1c still shows normal levels, this indicates that diabetic foot ulcers have been treated in DM disease control efforts, but the average grade is still high wherein GDP 180.95 (SD 71.4) mg/dl, 2 hours PP blood sugar with a mean value of 263.14 (SD 100.43) mg/dl, and HbA1c with a mean grade of 8.13 (SD 1.96). The three results of this examination meet the DM diagnostic criteria according to the Type 2 Control Consensus and Prevention of DM in Indonesia, where fasting blood glucose is more than 126 mg/dl, blood glucose 2 hours PP over 200 mg/dl and HbA1c> 6.5%.[2] This still high average value indicates that DM control, especially in diabetic foot ulcer patients, is still not optimal. Zubair et al study, suggesting that an increase in HbA1c value would cause a risk of diabetic foot ulcers, Singh et al, also suggests that DM has several complications and one of the most troubling is the occurrence of diabetic foot ulcers.[1,11]

HDL cholesterol levels have an average grade of 29.4 (SD 9.76), indicating that the mean HDL cholesterol level is below 40 mg/dl. This suggests that the treatment of dyslipidemia, especially HDL cholesterol in diabetic foot ulcers is not optimal, and may not even be done.

Assmann et al, in his journal, states that there is a weak association of HDL cholesterol with increased atherosclerosis, this is due to the potential effect of HDL cholesterol as antiatherogenic, through reverse cholesterol transport (RCT) mechanism, which takes cholesterol uptake in peripheral tissue by cholesterol HDL to the liver for later expression in the bile.[17] Wagner's pre-treatment classification showed that most cases were found in the Wagner 4 category (43.2%), even in Wagner 5 (13.5%). This is consistent with research conducted by Ikura et al. (2015), which has the most samples in the Wagner 4 and five classifications.[7]

After treatment there was a change in Wagner's classification where the highest number was at Wagner 1 (37.8%), Wagner 0 (13.5%) was found and no Wagner 4 and Wagner 5 were classified. This indicates that there has been an improvement on the severity of diabetic foot ulcers during treatment, where the condition of infection is reduced and no more patients with gangrene circumstances in the toes and soles.

HDL cholesterol levels in each Wagner classification before treatment and after treatment. At the time before treatment, the average patient had HDL cholesterol levels less than 40 mg/dl (n=34), which is a high risk for atherosclerosis according to AACE guidelines, and most often found in the classification of Wagner 4 (n = 16), and even Wagner 5 (n=5), while patients with HDL cholesterol 40-59 mg/dl were at moderate risk for atherosclerosis and found in Wagner 1 (n=3) classification.[18] After treatment, the average HDL cholesterol level increased, whereas patients with HDL cholesterol less than 40 mg/dl were reduced to 18 patients and 19 patients with HDL cholesterol 40-59 mg/dl, even found in Wagner 0 (n = 3). This suggests an improvement in HDL cholesterol and improvement in the severity of diabetic foot ulcers based on Wagner's classification after treatment. From both of these situations, i.e. at the time before treatment and after treatment showed that the lower the HDL cholesterol level, the higher the severity of diabetic foot ulcers based on Wagner classification.

Changes in HDL cholesterol during treatment where there was an average increase of 10.7 mg/dl and statistically significant with a value of p <0.001, as well as a change in Wagner classification during treatment where an average decrease of 2.05 and significant statistic with p-value <0.001. This suggests that there was an improvement during treatment where the average HDL cholesterol level increased and the Wagner classification decreased. The greater the level of Wagner classification fall the greater the increase in HDL levels, it can be seen the difference in the reduction of Wagner level 1 rating compared to 2 or 3 levels seen differences in HDL levels increase, the pattern of Wagner classification level decrease with increasing HDL cholesterol levels can be seen on the graph 1, but this is not statistically significant. This means that the reduced severity of diabetic foot ulcers based on Wagner's classification is not due to changes in HDL cholesterol levels alone, but there are other factors that influence during diabetic foot ulcer treatment such as blood sugar control, wound care, infection control and others, it is also possible because the number of research samples is less numerous to be able to more search for a correlation between changes in HDL cholesterol with the severity of diabetic foot ulcers.

Mendes et al, in his journal, said that in the handling of diabetic foot ulcers requires a team of metabolic, endocrine experts, surgeons, nurses, podiatrists, even sub-specialties such as vascular and orthopedic surgeons are also needed.[10] Treatment begins early in the diagnosis, including the decision to undergo hospitalization in patients with severe infection, deep ulcers involving bones and joints, and the presence of gangrene, requiring fluid resuscitation, control of the primary metabolic disorders of blood sugar levels requiring therapy insulin, infection control, and operative measures such as debridement if acquired necrosis, drainage, and possibly revascularization.

Previous studies have found a decrease in HDL cholesterol levels in acute phase conditions caused by the reduced half-life of apolipoprotein A-I (apo-I). It is also due to apoA-I catabolism in the liver and kidneys due to the release of apoA-I from HDL.[19] These conditions indicate the presence of vitrosus circulation where low HDL cholesterol levels due to diabetic foot ulcers will lead to progressive deterioration of diabetic foot ulcers.[19,20]

CONCLUSION

The authors concluded that there was a correlation between HDL cholesterol and diabetic foot ulcers severity based on Wagner classification at both early and after treatment, the lower the HDL cholesterol, the higher the severity of diabetic foot ulcers. There was a correlation between elevated HDL cholesterol levels during treatment with Wagner classification decrease during treatment, the higher the HDL change, the greater the Wagner classification, but this correlation was weak and not statistically significant. This means that the modification of Wagner classification was not only caused by the change of the increase of the level of HDL cholesterol. It was also affected by other factors during the treatment of diabetic foot ulcer, such as by the control of blood sugar, wound treatment, infection control.

Recommendation

Researchers recommend that any management of diabetic foot ulcers is not only controlled for their blood sugar levels but also on low HDL cholesterol levels above 60 mg/dl. To improve the health status of the public need to increase the standard operational management of diabetic foot ulcers therapy by completing laboratory tests, especially HDL cholesterol levels. Further research is needed to better understand the mechanisms of diabetic foot weights with low HDL cholesterol levels that may involve inflammatory biomarkers in association with atherosclerosis

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