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Research Article

CAN HIGH DENSITY LIPOPROTEIN (HDL) SERVE AS A MARKER OF RECOVERY TIME IN CELLULITIS?

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ABSTRACT

Background: Cellulitis of the foot contributes to morbidity in the diabetic population leading to considerable physical, physiological and financial burden not only for the patient but also for the community. Inflammatory markers like ESR and CRP, which are elevated, are non specific in identifying the severity of the disorder. We hypothesized that HDL which has a role in innate immunity can serve as a marker of severity.

Methods: Retrospective analysis of laboratory investigations on the day of admission of sixty three patients of diabetes with cellulitis of the lower limbs was performed. Depending on the severity and treatment of the cellulitis the population were categorized into two groups. Group I (n=31) included those patients who needed only antibiotics and regular dressing for their healing. Those patients with severe cellulitis needing debridement and skin grafting for recovery were placed in Group II (n=32).

Results: The prevalence and severity of cellulitis was more in males and also with duration of diabetes andpoor glycemic control. A significantly low HDL was seen in Group II, that had a negative correlation with recovery period (R^2 -0.7, $p<0.001$). A HDL cut off value of 17mg/dl, (95% CI 0.815 - 0.967, SE-0.039) was used to calculate relative risk of morbidity which was 3.75 times higher (95% confidence interval 2.00-7.02, $p<0.001$).

Conclusion: HDL in diabetic cellulitis may play a role in identifying the severity and hence can be used to change the modality of treatment thereby reducing morbidity.

INTRODUCTION

Cellulitis is a bacterial inflammation of tissues, usually superficial or subcutaneous[1]. The clinical severity of cellulitis can range from mild infection, to a severe necrotizing infection associated with a high mortality. Cellulitis is diagnosed clinically, with constitutional features and the appearance of local manifestations of inflammation. The most frequent site where cellulitis occurs is the leg and the common infective organisms are Streptococcus pyogenes and Staphylococcus aureus. Although the mainstay of treatment is antibiotics, severe cases also require debridement of the affected area and even skin grafting. One of the most important complications of chronic diabetes mellitus is cellulits and it would be apt to mention diabetes mellitus to be a risk factor for cellulitis [2,3]. Due to the absence of systemic manifestations like fever and leukocytosis and also due to the painless nature of the foot infection, diabetes with cellulitis often leads to high morbidity[4,5]. It is very much imperative that early identification of patients may be done to identify who would proceed towards severe cellulitis as it would reduce not only the physical trauma but also the pain of prolonged stay in the hospital.

One of the many mechanisms as to why diabetics are more prone to infection is defective innate immunity[6]. In most cases of cellulitis it is because of a breach in intactness of epithelial surface. CRPisa sensitive indicator of inflammatory and infectious disease process in a variety of diseases. However, using CRP as a biomarker in cellulitis has a number of disadvantages like a delayed release and low specificity. The predominant role of HDL has been that of an anti-atherogenicmolecule. Besides their role in lipid transport, lipoproteins contribute to innate immunity, which is the first line of host defense against invading microorganisms. There has been an increasing focus on the ability of lipoproteins, especially HDL to modulate an inflammatory response[7].

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Although studies have shown HDL to be low in patients with sepsis[8,9], we analyzed the role of HDL as a marker of morbidity and therefore estimating recovery time for patients with cellulitis.

MATERIALS AND METHODS

Retrospective analysis of data overaperiod of one year of diabetic patients with cellulitis who had been investigated for lipid profile was undertaken. Population considered for the study included individuals more than 18 years with cellulitis for the first time, diagnosed by the physician. Patients who had necrotizing infection and those who had started antibiotics prior to admission or with bilateral cellulitis were not included in the study.

After scrutiny of data sixty three patients of cellulits in the lower limbs were included in the study. The population was categorized into two groups depending on the final treatment which was given. The group I (n=31) included those patients of cellulitis who needed only antibiotics and regular dressing for their healing. Those patients with severe cellulitis needing debridement and skin grafting for recovery were placed in group II (n=32). All demographic and descriptive profiles along with blood investigations conducted at the time of admission was collected from laboratory records. The laboratory investigations included a complete blood count, erythrocyte sedimentation rate (ESR) along with fasting plasma glucose, renal function test, liver function test, lipid profile, C-reactive protein(CRP) along with HbA1C using Biosystems BA 400 autoanalyzer. Recovery was identified by an improvement in clinical symptoms and the complete recovery from edema, rash, tenderness and hotness of the skin and soft tissues. Recovery time was noted for all patients in accordance with the above guidelines.

Tests of normality was used to determine normal and non-normal distributions. Statistical significance of the difference between patients and controls were analyzed for each parameter by t test or Mann-Whitney test for numerical data and by Fischer's test for categorical data. The associations between variables were determined using Pearson's correlation analysis. Logistic regression analyses were performed to determine the independent associations between various parameters and HDL and recovery time. The value of HDL in predicting recovery time was evaluated by ROC curve. The results were expressed as relative risk with a 95% confidence interval.

RESULTS

Table 1 shows the descriptive profile of diabetic patients with cellulitis. Out of 63 patients, male subjects (n = 41) were more than female subjects (n = 23), indicating that 65% of the population were males. A similar distribution of gender was observed in both the groups of study population. The average age of the population was 48.6± 6.6 years with no significant change in the age in the two groups. The body mass index (BMI) observed in both the groups were of similar values. The mean duration of diabetes and duration of ulcer was higher in patients who required grafting(11.0±3.0years, 11.2 ± 2.0 weeks) than the group who could be treated with antibiotics(9.6 ± 2.8 years, 7.8 ±2.3 weeks, p=0.05 and p=0.01). There was a higher percentage of patients who were dependent on smoking, tobacco and alcohol in the group of patients who had severe cellulitis and thus required debridement and grafting. Smoking and chewing of tobacco was significantly associated with more severe degree of diabetic cellulitis. Fischer's exact test showed that the risk of requiring a graft was significantly associated with tobacco chewing (p=0.01) and smoking (p=0.05) in diabetic patients.

Table 1 Descriptive profile of diabetic patients with cellulitis

Parameters	Group I (n=31)	Group II(n=32)	P value
Age (years)	48.3 ± 6.1	49.0 ± 7.1	NS
Males (n)	19 (61 %)	22(66 %)	NS
Females (n)	12 (39 %)	11(34 %)	NS
BMI (kg/m²)	27.3 ± 2.6	27.7 ± 2.7	NS
Duration of diabetes (years)	9.6 ± 2.8	11.0 ± 3.0	0.05
Smoking habit (yes/no)	6/25	14/18	0.03
Tobacco chewing (yes/no)	11/20	22/10	0.008
Alcohol intake (yes/no)	8/23	9/26	NS

NS – not significant

Table 2 reveals that the most commonly measured indicators of general inflammation performed routinely within first hours of infection like total leukocyte count (TLC), erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP) are elevated in both the groups, which is significant higher in Group II. The renal and enzyme parameters like urea, creatinine, and alanine and aspartate amino transaminases (ALT and ALT) were within normal limits. There was a rise in fasting plasma glucose (FPG) in both the groups the rise being more in that group which required grafting (p=0.02). A similar change was also observed in the glycatedhemoglobin (HbA1C) (p=0.04). When comparing the lipid profile parameters; total cholesterol and LDL was significantly high in cases when compared to the group which served as controls (p=0.006, p=0.001). The HD Llevel was significantly lower in the group requiring grafting than in the control group (p=0.00). However, there was no significant difference between mean serum triglyceride (p=0.13) between the groups.

Table 2 Biochemical profile of diabetic patients with cellulitis. Data are expressed in mean ±SD

Parameters	Group I (n=31)	Group II(n=32)	P value
TLC(× 10 /L)	11.2 ± 2.2	13.3 ± 2.4	0.001
ESR (mm/h)	35.6 ± 14.0	59.5 ± 12.7	0.001
CRP(mg/dl)	24.2 ± 9.5	53.8 ± 9.9	0.001
FPG(mg/dl)	176.3± 58.1	211 ± 62.4	0.02
Urea (mg/dl)	38.6 ± 9.9	36.1 ± 8.4	0.28
Creatinine(mg/dl)	0.9 ± 0.4	0.8 ± 0.4	0.32
AST (IU/L)	34.6 ± 11.4	33.1 ± 12.7	0.62
ALT (IU/L)	35.1 ± 13.7	32.7 ±10.5	0.43
TC (mg/dl)	216.54 ± 43.6	245.12 ± 37.0	0.006
TG(mg/dl)	202.7±43.6	188.3 ± 40.5	0.138
HDL (mg/dl)	41.1 ± 6.0	15.2 ± 6.15	0.001
LDL(mg/dl)	134.8 ± 44.5	192.2 ± 37.0	0.001
HbA1C (%)	7.7 ± 1.2	8.4 ± 1.5	0.04

There was positive correlation of recovery time with BMI(r=0.216,p=0.08), FPG(r=0.20, p=0.11), CRP(r=0.427, p=0.00), total cholesterol(r=0.123, p=0.34) and LDL(r=0.203, p=0.11). HDL registered a negative correlation with BMI(r=-0.65, p=0.0001), FPG(r=-0.22, p=0.080), CRP(r=-0.350, p=0.007), LDL(r=-0.30, p=0.016), cholesterol(r=-0.164, p=0.195) (Table 3).

Table 3 Correlation coefficient (Pearson's) between HDL, recovery time and measured parameters

	HDL levels		Recovery time	
Parameters	**R value**	**P value**	**R value**	**P value**
HDL	-	-	-0.481	0.001
BMI	- 0.196	0.234	0.216	0.08
CRP	- 0.35	0.007	0.427	0.000
FPG	- 0.22	0.08	0.20	0.11
TC	- 0.16	0.210	0.123	0.34

Pearson's correlation analysis indicated significant negative correlation of HDL with recovery time indicating an increase in morbidity when the HDL is low at time of admission (correlation coefficient -0.837, p=0.00). For every 1mg/dl decline in HDL, the duration of recovery is increased by 1.42 days (R^2=70%). (Figure 1)

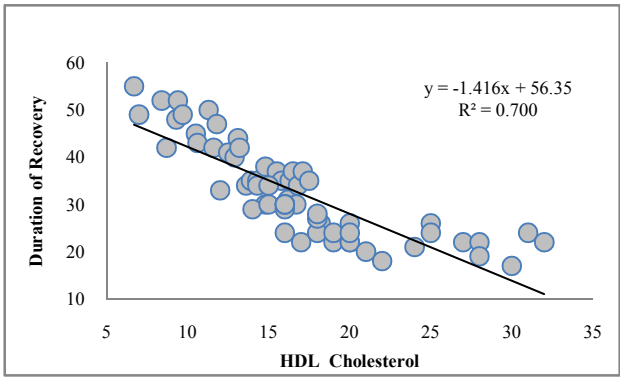

Figure 1 Correlation graph of recovery period with HDL cholesterol

Area under ROC for HDL was 0.891(95% CI 0.815 - 0.967) with standard error of 0.039 (Figure 2). A HDL cut off value of 17 mg/dl had a sensitivity of 90.6% and specificity of 67.7%. Significant association was seen between morbidity and <17 mg/dl HDL level on day 1 with Pearson Chi-Square = 22.1, df =1 and p<0.001. Relative risk of morbidity in patients with day 1 HDL <17 mg/dl was 3.75 times higher than patients whose HDL values were ≥ 17 mg/dl (95% confidence interval 2.00 – 7.02, p<0.001).

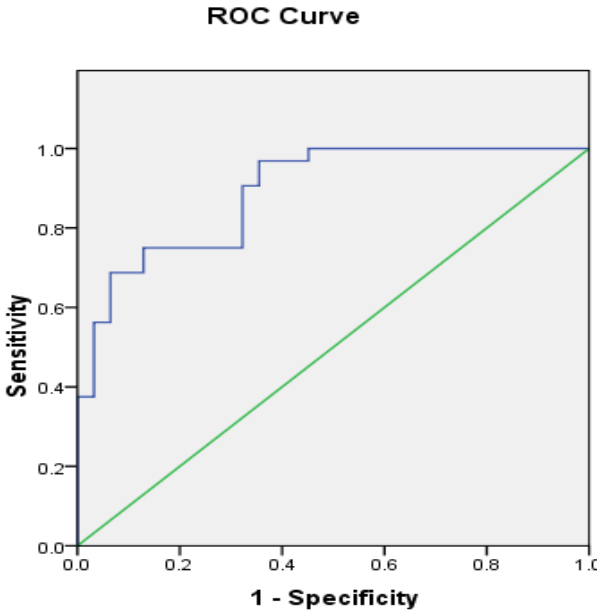

Figure 2 ROC curve of HDL with cellulitis

DISCUSSION

Cellulitis is a common complication of diabetes mellitus, with involvement of the lower limb, i.e, foot which is observed in approximately 15% of patients during their lifetime[10]. They are also a major cause of hospital admissions affecting morbidity and posing economic threat to the individual. The patient population chosen were all those who had cellulitis due to diabetes which had affected the lower limb. Various reasons attributed to this site of cellulitis are walking barefoot, poor socioeconomic conditions and lack of proper knowledge and education for diabetes care.

The occurrence of diabetic cellulitis noted was mostly in males and in the middle aged population. Similar demographic data was seen in study conducted by others[11]. In India, since males make up a larger share in being the bread earner for the family, their affliction affects the economic burden of the family. Also associated with it are the psychosocial effects on the patient's quality of life and loss of productivity. On comparison of BMI, it was found that it was similar in both the groups, similar to what majority of literature have shown that there is no significant association between diabetic foot ulcers and BMI[12,13]. As the duration of diabetes in an individual progressed it was associated with a higher rate of complications, which explains our findings in Group II having severe cellulitis. Studies have shown that a duration of diabetes ≥ 10 years was a significant risk factor for foot ulcers[14]. This could be explained by longer duration of diabetes have a higher rate of complications like neuropathy[15], which is responsible for severity of complications.

Findings pertaining to the habits of smoking, intake of tobacco and alcohol, studies have shown that smoking and intake of tobacco increases the risk as well as grade of foot ulcers in diabetics[11,14]. This study documented smoking and intake of alcohol to be in all males, which could be due to the fact that both these are not socially acceptable in our society. Smoking and chewing of tobacco significantly increased the severity of foot ulcers in this population. Although exact reasons are not known smoking and chewing of tobacco are associated with poor wound healing. Tissue hypoxia, toxins like nicotine, carbon monoxide and cyanide affect the vascular system and wound microenvironment by reducing functionality of red blood cells, white blood cells (WBC) especially neutrophils and lymphocytes, cytotoxicity of natural killer cells, collagen synthesis and fibroblast activity[16]. About 30% of the participants were taking alcohol, however it was not related to the severity of the cellulitis. Severe grade of cellulitis mounted an elevated WBC, showing the inflammatory response of bone marrow to degree of infections. Acute phase reactants, like erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are markers of inflammation and elevated in response to severity of infection, yet these are non-specific in nature.

An assessment of metabolic panel of tests like liver function test and renal function test revealed to be within normal limits in both groups. Fasting blood glucose and HbA1c were significantly above normal limits in both groups indicating a poor glycemic control. Hyperglycemia forms advanced glycation end products (AGE) which induce inflammatory molecules like TNF-αand IL-1 and interfere collagen synthesis[17]. Also keratinocytes change in their morphology,

proliferation ability and differentiation pattern when exposed to high glucose[18]. Glucose control is an essential prerequisite for wound healing.

The changes in lipid profile which is a feature of insulin resistance, i.e., higher cholesterol, elevated LDL particles and triglycerides and reduced HDL cholesterol levels was observed in the study population. This is primarily due to altered metabolism of triglyceride rich lipoproteins in diabetes mellitus. The decline in HDL which normally occurs in diabetes is because of increased transfer of cholesterol from HDL to triglyceride rich-lipoproteins with reciprocal transfer of triglyceride to HDL. Such HDL particles are hydrolyzed by hepatic lipase and are cleared from plasma[19]. The other reason for a decline in HDL could be due to the negative phase inflammatory response. HDL binds and neutralizes lipopolysaccharides (LPS) released from gram negative bacteria, which are then rapidly cleared from the plasma. Similarly lipoteichoicacid (LTA) released by gram positive bacteria, are associated with HDL in circulation and are cleared from circulation[20].

The results of the present study indicate that the HDL correlates in markedly contradiction with CRP and recovery time. Thus HDL may be an effective marker for estimating the recovery time of patients with cellulitis. The strong negative correlation of between CRP and HDL can make CRP a useful marker of severity and HDL to function as marker of recovery time. The significant negative correlation of HDL at time of admission with recovery period indicates the high burden of endotoxin in patient affecting the recovery. Thus steps can be taken to improve the serum HDL level alleviate morbidity and aid recovery. Studies have highlighted the role of r-HDL (recombinant HDL)as a potent inhibitor of TNF-α from gram negative bacteria. From the above study we found that HDL level of 17mg/dl can serve as a cut-off mark to predict the outcome of the disease. HDL by promoting LPS and LTA detoxification, restrain the response of inflammatory cells thereby holding back the activation of endothelial cells. HDL normally plays the role of a multi protective agent against endothelial dysfunction in cellulitis. Strategies for raising HDL can be put forth along with routine treatment for the patients. Although lifestyle modification like proper diet, weight reduction, physical activity, cessation of smoking chewing tobacco and alcohol consumption are advised, pharmacological management therapy to uplift HDL and HDL replacement therapy through HDL or Apo A1 mimetic peptides can be tried to diminish the morbidity in these patients.

The limitations of this retrospective study can be improved by conducting a prospective study in a large population, wherein after noting the baseline characteristics, a HDL trend can be assessed. Similarly the parameters at the time of discharge can also be evaluated to note the changes that occur when the patients are recovering.

CONCLUSIONS

A decline in HDL is associated with raised severity in diabetic cellulitis and therefore can be utilized control morbidity. Efforts should also be directed in controlling various risk factors which affect the severity of the disease. Although therapeutic interventions can be introduced to raise HDL level, raising HDL to improve glycemic control and reduce cardiovascular risk should be targeted through weight reduction, increased physical activity and stopping of smoking, alcohol and tobacco.

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