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*Full length Research paper*

# Evaluation of serum leptin levels in obese local Libyan female subjects at Benghazi- Is cluster analysis a better evaluator method for such a study

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**Obesity related diseases like diabetes and coronary artery disease (CAD) are very much prevalent in local Libyan population at Benghazi. Leptin is one of the adipocytokines implicated in fuel balance as well as a marker of obesity. Leptin resistance is considered to be one of the risk factors associated with CAD. Therefore the present study was undertaken to evaluate the presence of leptin resistance in obese females in local population. The study was undertaken in female obese (measured by Body Mass Index) and non-obese patients. The patients were grouped into two groups of patients; one with BMI< 25(G1) and the other with BMI>30(G2). The results obtained were analyzed according to groups classified as obese and non-obese subjects as well as by cluster analyses. Cluster analysis is an important technique in many research areas such as data mining, information science agriculture technology, and biomedicine. One of the most important issues in cluster analysis is the evaluation of clustering results to find the partitioning that best fits the underlying data. The data obtained was subjected to cluster analysis using Silhouette index: The assumption made was obese people will have more leptin levels or leptin resistance. This assumption generalizes and assumes obesity is the cause or effect of leptin resistance. But when the results are used in adopting cluster analyses there was no assumption or classification of patients based BMI. Rather the results obtained were correlated to bring out the relationship between obesity and leptin resistance. In the present study cluster analyses did bring about similar observations made in the independent variables (biochemical parameters) as observed in groups classified based on BMI. Cluster analyses seem a better approach to say that BMI or obesity could be a risk factor for leptin resistance and will help undertake a prospective cohort studies extended more to patients with obesity, leptin resistance and future coronary artery disease (CAD).**

**Key words:** Leptin, body mass index (BMI), obesity, cluster analyses, Silhouette index.

## INTRODUCTION

In the Arab world an epidemiological study is usually done to understand the prevalence of a disease in a more homogenous community with a view to plan pre-ventive measures. Libyan Arab Jamahiriya is a uni-que country where cities are built around a particular sect or a tribe. To undertake any public health measures in such community an understanding of a cause and effect may prove beneficial. For example diabetes and coronary artery disease (CAD) are very much prevalent in Benghazi (Beshyah, 2010). One of the known causative factors of diabetes and CAD is obesity. Obesity is a global health problem and is associated with insulin resistance (IR) . Therefore adipose tissue has become the prime focus of research as it is known to be lipoprotective organ. One of the adipocytokines known to influence body composition and therefore adiposity is Leptin (Zhang et al., 1997; Sattar et al., 2009).

Leptin has been shown to play a significant role in fuel balance modulating body weight in a person. As a routine observational study and to understand the leptin status in a local population the present study was undertaken by selecting the study subjects based on their body mass

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index (BMI). It is assumed that an increase BMI acts as a marker for obesity. A BMI <25 is taken as normal and a BMI> 25 is taken as obesity. The assumption is that Leptin levels will be normal or low in people with normal BMI and will be high in BMI>25. Testing such a hypothesis in a defined population may bring out the cause-effect relationship between BMI and Leptin. But the shortcoming of such a study will be the predetermination of body weight as a cause for leptin increase or leptin resistance (Hill, 1965). Such a predetermined or predictive variable will carry a bias that people with normal BMI will not have leptin resistance. That will result in the lookout for changes only in obese subjects expecting no such change in leptin levels than in non obese subjects. There is growing evidence which suggests that obesity is a mechanism to protect the body from harmful effects of lipotoxicity (Sheriff and Elshaari, 2010). Adipose tissue by storing more fats may block the entry of glucose which may cause glucose intolerance. Glucose intolerance over a period of time may affect the insulin sensing mechanism in Beta cells as well as in insulin action in target organs such as liver. In other words the transition from protective role of obesity to lipotoxicity may depend possibly upon leptin sensitivity as well as genetic predisposition. In such circumstances along with the routine case-controlled studies cluster analyses may help to rule out such a bias and help bring out meaningful explanation to obesity protective or toxic role in a study population (Benson and Hartz, 2000; Concato et al., 2000). With this view in mind the following study was carried out in a local population to evaluate leptin status in normal and obese subjects. The groups selected were based on BMI and the results obtained based on such grouping is objectively analyzed with cluster analysis using a software program. Silhouette index indicates a better overall quality of the clustering (Kaijun et al., 2009).

Cluster analysis is an important technique in many research areas such as data mining, information science agriculture technology, and biomedicine. One of the most important issues in cluster analysis is the evaluation of clustering results to find the partitioning that best fits the underlying data (Halkidi et al., 2001). For the evaluation of clustering solutions, it is usually the validity indices that are used to measure the quality of clustering results. There are two kinds of validity indices: i) external indices and ii) internal indices. An external index is a measure of agreement between two partitions where the first partition is a priori known clustering structure, and the second results from the clustering procedure (Dudoit and Fridlyand, 2002). Internal indices are used to measure the goodness of a clustering structure without external information. For external indices, we evaluate the results of a clustering algorithm based on a known cluster structure of a data set (or cluster labels). For internal indices, we evaluate the results using quantities and features inherent in the data set. The optimal NC is usually determined based on an internal validity index. Silhouette index: A composite index reflecting the compactness and separation of clusters; a larger average Silhouette index indicates a better overall quality of the clustering result, so the optimal NC is the one that gives the largest average Silhouette value (Kaufman and Rousseeuw, 1990; Chen et al., 2002). The aim of the study is to emphasize that application of cluster analyses will be a better approach in such cases.

## MATERIALS AND METHODS

Cluster analysis produced several grouping sets. According to the Silhoite index (Kaijun et al., 2009) the best grouping obtained, produced 2 groups with an index value of 0.6. The mean ± SD and the median was calculated for each parameter (age, body mass index (BMI), Waist circumference (WC), high sensitive C-reactive protein (hsCRP), Leptin, cholesterolstate the parameters) within each group. In addition, the means for each parameter were compared using student's T-test between the two groups using SPSS software package.

The same patient were divided into two groups based on each patient's BMI value to achieve the purpose of this study which is comparing cluster analysis system to a more classical way of grouping patients. Statistical analysis was carried out as for grouping using cluster analysis.

## RESULTS

Results for cluster analysis and BMI grouping are expressed in Tables 1 and 2. Comparing the means of the measured parameters of patients clustered in group G2 to those clustered in group G1 revealed that they have significantly higher age, BMI, WC (Body Mass Index, Waist Circumference) and leptin. On the contrary CRP (High sensitive C-reactive Protein) was significantly lower in group G2 compared to G1. Cholesterol, on the other hand did not show any significant differences between the two groups. It is noteworthy that grouping according to the BMI produced a similar trend in values for each parameters within group G2 (BMI) compared to group G2 (cluster).

The data for the 2 groups separated based on the BMI value are expressed in Table 2. Comparing the means of the measured parameters of patients in the 2 group (G2 to G1-based on BMI value) revealed that patients in group G1 have a significantly higher mean for age, WC and leptin. On the contrary CRP was significantly higher in group G2 compared to G1. Cholesterol, on the other hand did not show any significant differences between the two groups.

## DISCUSSION

In medicine, a cohort study is often undertaken to obtain evidence to try to refute the existence of a suspected association between cause and effect; failure to refute a

**Table 1.** Cluster analysis produced several sets of groups and each clustering set has its own clustering significance index (the Silhoite index). The highest index obtained produced 2 groups. Mean ± SE and the median for each parameter, in addition to the level of difference significance between the two groups, are shown in this table.

| Factor group | Group G2 | Group G1 | | Sig. | |
|---|---|---|---|---|---|
| | Median | Mean ± SE | Median | Mean ± SE | |
| Age | 37 | 36±1 | 28 | 31±3 | 0.110 |
| BMI | 37 | 39±1 | 27 | 27 ± 0.8 | 0.002 |
| CRP | 1 | 2±0.3 | 8 | 9 ± 1 | 0.000 |
| WC | 113 | 111±3 | 80 | 81 ± 2.5 | 0.000 |
| Leptin | 44 | 46±4 | 14 | 16±2 | 0.000 |
| Cholesterol | 154 | 149±5 | 157 | 165±5 | 0.219 |

Statistically significant at the level between Mean±SE. *P<0.05. **P<0.001.

**Table 2.** Results for cluster analysis and BMI grouping are expressed

| Factor group | | Comparison of means Mean ± SE | P |
|---|---|---|---|
| Age (years) | G1 | | |
| | G2 | | |
| BMI (kg/m$^2$) | G1 | 36.085 ± 0.94 | 0.000** |
| | G2 | 22.626 ± 0.44 | |
| Waist Circumference (cm) | G1 | 104.32 ± 2.34 | 0.000** |
| | G2 | 69.700 ± 3.13 | |
| Serum Leptin (ng/ml) | G1 | 36.482 ± 3.18 | 0.000** |
| | G2 | 11.950 ± 1.92 | |
| Total cholesterol (mg/ 100 ml) | G1 | 160.65 ± 5.66 | .036* |
| | G2 | 140.35 ± 7.49 | |

Statistically significant at the level between Mean±SE. *P<0.01. **P<0.001.

hypothesis strengthens confidence in it. Crucially, the cohort is identified before the appearance of the disease under investigation. The study groups, so defined, are observed over a period of time to determine the frequency of new incidence of the studied disease among them. The cohort cannot therefore be defined as a group of people who already have the disease. Prospective (longitudinal) cohort studies between exposure and disease strongly aid in studying causal associations, though distinguishing true causality usually requires further corroboration from further experimental trials (Benson and Hartz, 2000).

The question that can be answered by the use of a cohort study is: does adiposity measured as BMI to X (say,) correlate with outcome Y (say, coronary artery disease)? Such a study would recruit a group of obese people and a group of non-obese (the unexposed group) and follow them for a set period of time and note differences in the incidence of coronary artery disease (CAD) between the groups at the end of this time. The groups are matched in terms of many other variables such as economic status and other health status so that the variable being assessed, the independent variable (in this case, obesity and leptin levels) can be isolated as the cause of the dependent variable (in this case, CAD) (Concato et al., 2000). In this example, a statistically significant increase in the incidence of CAD in the obese group as compared to the non-obese group is evidence in favour of the hypothesis. However, rare outcomes, such as CAD are generally not studied with the use of a cohort study, but are rather studied with the use of a case-control study.

Shorter term studies are commonly used in medical research as a form of clinical trial, or means to test a particular hypothesis of clinical importance. Such studies typically follow two groups of patients for a period of time and compare an endpoint or outcome measure between the two groups

A "prospective cohort" defines the groups before the study is done, while a "retrospective cohort" does the

grouping after the data is collected. Whereas prospective cohorts should be summarized with the relative risk, retrospective cohorts should be summarized with the odds ratio. An example of a retrospective cohort is long-term mortality after gastric bypass surgery (Margetts et al., 1995; Yamin and Sarah, 2010). The present study does ask a question whether obesity is related to leptin resistance or BMI is related to Leptin levels.

The study was undertaken in female obese (measured by body mass index) and non-obese patients. The patients were grouped into two groups of patients; one with BMI< 25 and the other with BMI>30. The assumption made was obese people will have more leptin levels or leptin resistance.

The assumption was that all obese people will have leptin resistance. This assumption generalizes and assumes obesity is the cause or effect of leptin resistance. But when the results are used adopting cluster analyses there was no assumption or classification of patients based BMI. Rather the results obtained were correlated to bring out the relationship between obesity and leptin resistance. In the present study cluster analyses did bring about similar observations made in the independent variables (biochemical parameters) as observed in groups classified based on BMI.

Cluster analyses seem a better approach. This to say that BMI or obesity could be a risk factor for leptin resistance and will help undertake a prospective cohort studies extended more to patients with obesity, leptin resistance and future coronary artery disease (CAD).

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