**Original Research Article**

# Effect of lifestyle modification on serum myostatin levels in prediabetics a prospective study

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**A R T I C L E   I N F O**

**A B S T R A C T**

**Introduction:** Prediabetes is an insulin resistant state where blood glucose levels are higher than normal but not high enough to be classified as Diabetes. Lifestyle modifications such as diet and physical exercise can prevent its progression to Type 2 diabetes. The adipose tissue and skeletal muscle are dependent on insulin for glucose uptake. Myostatin is a myokine known to restrict muscle growth by activation of SMAD(homologues of the Drosophila protein, mothers against decapentaplegic (Mad) and the Caenorhabditis elegans protein Sma signaling pathways). Myostatin expression is down regulated by exercise and weight loss. Myostatin levels have been shown to be increased in the causal pathway of acquired insulin resistance associated with physical inactivity. Increased serum Myostatin levels also are seen in cancer and obesity.
**Objectives**: To assess the effect of lifestyle modification on Myostatin levels in patients with pre-diabetes and to correlate the same with insulin resistance.
**Materials and Methods:** After obtaining ethical clearance from Ethics Committee of the Institute, 40 pre-diabetics visiting the Ramaiah Medical Hospital for treatment were included in the study. With their consent, blood samples were drawn for estimation of FBS, Insulin and Myostatin. The patient was advised moderate intensity physical activity comprising of brisk walk for 150 minutes a week for a period of 3 months. They were called for a follow up after 3 months and blood samples were drawn for estimation of FBS, Insulin and Myostatin.
**Results and Conclusion:** Serum Myostatin levels decreased significantly in individuals who exercised (P-value of 0.002) and increased in individuals who did not exercise with a P-value of 0.048. Serum Myostatin appears to be a promising biomarker to objectively assess lifestyle modifications introduced in pre-diabetics.

## 1. Introduction

Diabetes Mellitus is currently one of the biggest health concerns that the world is facing today. The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances in carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs.[1]

India has been called "the diabetes capital of the world," and it is estimated that 41 million Indians have the disease and "every fifth diabetic in the world is an Indian". The prevalence of impaired glucose tolerance test (GTT) ranges from 3.6–9.1 per cent, which indicates a potential of further increase in the prevalence.[2] Indians are more prone to Type 2 Diabetes Mellitus due to their genetic makeup, food habits (rich in carbohydrates and fat) and sedentary lifestyles. More number of working hours and health care facilities are lost tending to the morbid complications resulting due

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to diabetes mellitus.  It is pertinent to prevent the onset of the condition at the primordial level and thereby improve the quality of life.

A Pre-diabetic state results when the blood sugar level is higher than normal but yet not high enough to be classified as Type 2 Diabetes Mellitus.   Without the appropriate interventions the individual has a high likelihood of developing Type 2 Diabetes Mellitus in the near future.   With an increasing awareness amongst the general population, when subjected to screening campaigns, more individuals can be identified in pre-diabetic state. They can be counseled to undergo life style modifications like diet and exercise.

Type 2 Diabetes Mellitus is most often due to insulin resistance. Skeletal muscles and adipose tissue are the main sites for insulin dependent glucose uptake, when the blood glucose levels are high.  While treating a pre-diabetic, the aim would be to improve insulin sensitivity.

It has been observed that there is an interplay between cytokines secreted by the adipose tissue, muscle and liver towards the development of Insulin resistance.

Many exercise induced myokines are being implicated. One such down regulated molecule that has been studied is Myostatin.  The beneficial effects of exercise have been known to decrease insulin resistance.  Studies are still being done to explain the exact mechanism.

Myostatin is a member of the transforming growth factor beta family of secreted growth factors and is a significant negative regulator of skeletal muscle development and size. Knock-out in the Myostatin gene has led to dramatic increase in muscle mass in animals.  Myostatin binds to its cell surface receptors, Activin receptor type II or IIb, and activates intracellular members of the SMAD family of signalling proteins, which then translocate to the nucleus and regulate transcription thus decreasing the muscle size.[3]

There is experimental evidence showing that Myostatin directly regulates glucose metabolism by promoting glycolysis and glucose uptake, as well as decreasing glycogen content through activation of AMPK pathway. Increased levels of Myostatin in cancer patients has led to attributing Myostatin for cancer cachexia.[4]

Exercise and weight loss results in a downregulation of Myostatin mRNA and an improvement in insulin sensitivity in obese older men and women.  Myostatin inactivation appears to potentiate the beneficial effects of endurance exercise on metabolism.   Many of these effects appear to be indirect consequences of the effects of Myostatin inhibition on skeletal muscle growth, increas ing the lean tissue metabolic platform available for glucose and fatty acid uptake and utilization.[5]

Myostatin mRNA levels were decreased in muscle and adipose tissue from ob/ob mice upon two weeks of daily injection of recombinant leptin , and also decreased in muscle biopsies from obese human patients following weight loss due to either biliopancreatic diversion or gastric bypass surgery.[5]

Increased myostatin levels have been shown to be in the causal pathway of acquired insulin resistance associated with physical inactivity. Both muscle and plasma myostatin protein levels are regulated by aerobic exercise.[6]

Myostatin inhibition suppresses inflammation, increases Irisin production, increases fatty acid oxidation and the browning of WAT (white adipose tissue) to reduce free fatty acids (FFA) while improving insulin sensitivity.[7]

This study intends to evaluate the usefulness of estimating serum Myostatin levels in pre-diabetics to prevent the progression to overt Type 2 Diabetes Mellitus.

## 2.   Materials and Methods

It was a follow -up study which included 40 newly diagnosed Pre Diabetic patients visiting M S Ramaiah group of hospitals with Fasting Blood Glucose levels of 100 mg/dL to 125 mg/dL OR 2-h Post-prandial glucose in the 75-g OGTT between 140 mg/dL to 199 mg/dL OR Hb A1c in the range of 5.7–6.4%.[8] Samples were collected over a period of 6 months starting from June 2016.  Patients with renal disease, heart diseases, acute inflammatory conditions, liver diseases, malignancy, pregnancy, hypertension, Diabetes Mellitus, those undergoing surgery, those who are on any medications like corticosteroids, oral contraceptive pills, progesterone, epinephrine, olanzapine, thiazide diuretics and individuals who are on regular exercise were excluded. After a detailed explanation, consent was obtained and blood samples collected from each study subject.   The blood samples were centrifuged, the serum was processed immediately for estimation of Glucose by Hexokinase method, HDL by Direct measure(PEG) method, Total Cholesterol by Cholesterol oxidase, esterase, peroxidase method, Triglyceride by enzymatic with glycerol blank method and LDL by Direct measure method. Blood with EDTA was used for $HbA_{1C}$ quantitation by HPLC (High Performance Liquid Chromatography) method. The serum samples were then stored at -70 degree C, until analysis, for estimation of Myostatin and Insulin.  Both these analytes were estimated by Enzyme Linked Immunosorbent Assay (ELISA) kit method. Waist to hip ratio was measured at the level of umbilicus as an anthropometric index. The Insulin resistance was calculated using the HOMA-IR calculator.

As a follow-up measure, these patients were advised moderate intensity physical activity like brisk walk for 150 minutes a week (30 minutes each day for at least 5 days a week) for a period of 3 months after which the study individuals were called back for review again.   Serum Myostatin, serum Insulin, serum glucose, serum Total cholesterol, HbA1c and waist to hip ratio were measured by the methods mentioned above.

## 3. Results and Discussion

Out of the 40 individuals included in the study 21 individuals followed the life style modifications advised (Group 1) while 19 of them did not (Group 2). The results were entered into the excel sheet and analysed with SPSS software (Statistical Package for the Social Sciences) version 20. The continuous variables were summarized by employing descriptive statistics such as mean, standard deviation and interquartile range. All the categorical data were presented using numbers and percentages. Waist circumference, Fasting blood sugar, Total cholesterol showed parametric distribution. Triglycerides, HDL, LDL, Insulin, Insulin resistance and Myostatin had nonparametric distribution. Kolmogorov-Smirnov Test was used to examine distribution of different tests.

The differences between the before and after values of variables were computed and compared across the 2 groups using Mann Whitney test and t test.

Statistical significance was interpreted as strongly significant (if P value≤0.01); Moderately significant (if P value > 0.01 to ≤ 0.05); Suggestive significance (if P value >0.05 to <0.1)

Chi-Square Test was used to compare age and sex distribution between the two groups and there was no statistically significant difference.

The waist circumference in group 1 individuals decreased after lifestyle modification but increased in Group 2 individuals. The difference between the 2 groups was statistically significant with a P value of 0.010.

The Fasting Blood Glucose levels had parametric distribution; the mean values decreased in Group 1 after lifestyle modification and were statistically significant when compared with Group 2 persons with a P value of 0.007.

The values obtained for Total cholesterol had parametric distribution, the mean values in Group 1 subjects decreased after following lifestyle modifications but increased in Group 2 individuals. This was statistically significant with a P value of 0.010.

The Triglyceride levels had nonparametric distribution; the median values decreased after lifestyle modifications in group 1 with a suggestive statistical significance when compared to Group 2.

The HDL levels had a non-parametric distribution and did not show any significant difference between the two groups (P value of 0.88).

The LDL levels showed non parametric distribution and the median values decreased in Group 1 after lifestyle modification in comparison to group 2. T he decrease was statistically significant with a P value of 0.004.

The values obtained for Insulin and Insulin Resistance showed a non-parametric distribution and the median values decreased in Group 1 in comparison to Group 2. The difference was found to be statistically significant with a P value of .017 and 0.01 respectively.

Myostatin levels showed nonparametric distribution and the median values show a decrease in Group 1 after lifestyle modification; when compared with Group 2. It was found to be strongly statistically significant with a P value of <0.001.

The difference between the values obtained for first (before initiating lifestyle modification) and second set (after introducing lifestyle modifications) for Myostatin correlated with that of Fasting Glucose levels with a P value of 0.009 in Group 1 individuals

The difference between the values obtained for Myostatin, in the subjects prior to introduction of lifestyle modification and on following lifestyle modification, correlated with that of Fasting Glucose levels and Total Cholesterol levels with a P value of 0.007 and 0.004 respectively, in Group 2 individuals.

## 4. Discussion

Subjects in group I are those that followed the exercise regime as a life style modification.

There was a statistically significant reduction in waist circumference (P value 0.01) and FBS (P value 0.007) in these individuals when compared to group 2 who did not comply to lifestyle modifications. Kimberley L. Way et al state in their study that exercise increases translocation of insulin-mediated glucose transporter type 4 (GLUT4) to the sarcolemma, therefore transiently increasing the glucose uptake. There is an increase in the expression of GLUT4 mRNA which is seen to persist for 3 to 24 hours after exercise which translates to increase in GLUT4 protein expression resulting in increased glucose uptake.[9] Rynders CA found a decrease in serum glucose levels in Pre-diabetics even after a single bout of exercise.[10]

Total cholesterol levels in group 1 individuals reduced significantly (P value 0.010) after exercise. John Skoumas et al found an inverse relationship between physical activity and total cholesterol levels.[11] The triglyceride levels decreased in group 1 but it was of suggestive statistical significance. The increase in demand for energy in the muscle during sustained moderate exercise leads to utilization of fatty acids by beta oxidation which reduces the triglyceride levels. The researchers found that when participants had lower baseline levels of TGL, there was only a slight decrease in TGL after exercise. Wang Y et al in their study found that there was only a mild reduction in Triglyceride level when the base line Triglyceride level was low while a significant reduction was seen if the base line level was high especially in sedentary workers. Implying that baseline Triglyceride levels influence the exercise induced reduction of the same.[12]

The LDL cholesterol levels decreased in group 1 after regular exercise with a P value of 0.004 which was strongly statistically significant. The HDL cholesterol levels increased in group 1 after exercise but it was not found to be statistically significant. Several studies undertaken

**Table 1:** Comparison of variables

|  | Total | group 1 | group 2 | P-value |
|---|---|---|---|---|
| Sex M/F (%) | 23/17 (57%/43%) | 14/7 (66%/34%) | 9/10 (47%/53%) | 0.361 |
| Age (M & SD) | 46.23 (4.61) | 45.57 (4.75) | 46.95 (4.61) | 0.359 |

**Table 2:** Comparison of variables

| Variable | Group 1 Before | After | Group 2 Before | After | P value |
|---|---|---|---|---|---|
| **WC** (cms) | 88.29 | 87.14 | 88.58 | 89.92 | 0.010 |
| (M &SD) | (3.00) | (2.98) | (2.55) | (2.52) |  |
| **FBS** (mg/dl) | 110.95 | 100.52 | 110.37 | 110.68 | 0.007 |
| (M & SD) | (7.24) | (10.9) | (7.30) | (10.49) |  |
| **TC** (mg/dl) | 185.0 | 173.4 | 174.42 | 190.37 | 0.010 |
| (M & SD) | (35.12) | (36.75) | (30.34) | (33.56) |  |
| **TG** (mg/dl) | 178 | 148.0 | 143.0 | 168.0 | 0.052 |
| (Md & IQR) | (97.0-315.0) | (81.5-314) | (84.0-289.0) | (99.0-263) |  |
| **HDL** (mg/dl) | 37 | 37.50 | 33.00 | 40.0 | 0.88 |
| (Md & IQR) | (30.0-44.0) | (32.75-52.50) | (28.5-56.0) | (31.75-48.50 |  |
| **LDL** (mg/dl) | 130.0 | 119.50 | 120.0 | 133.0 | 0.004 |
| (Md & IQR) | (107.3-154.3) | (89.50-135.00) | (111.0-142.0) | (117.50-146.50) |  |
| **INS** (mIU/L) | 3.20 | 0.50 | 1.20 | 1.60 | 0.017 |
| (Md & IQR) | (1.45-6.74) | (0.20-0.85) | (0.40-4.70) | (.60-4.60) |  |
| **IR** (Md & IQR) | 0.829 | 0.14 | 0.69 | 1.60 | 0.010 |
|  | (0.37-2.34) | (0.1-0.23) | (0.15-1.82) | (0.60-4.60) |  |
| **MYO** (ng/ml) | 102.50 | 46.0 | 55.50 | 67.50 | <0.001 |
| (Md & IQR) | (56.25-326.7) | (36.50-101.5) | (35.5-271.00) | (47.50-295.50) |  |

**Table 3:** Pearson ccorrelation of differences between the before and after values of Group 1

| Groups |  |  | DIFF_Myos | DIFF_WC | DIFF_FBS | DIFF_TCHOL | DIFF_TG | DIFF_HDL | DIFF_LDL | DIFF_INS | DIFF_IR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | DIFF_Myos | r | 1 | .348 | .557** | .017 | .025 | .080 | .030 | .202 | .255 |
|  |  | p |  | .122 | .009 | .943 | .915 | .732 | .897 | .379 | .265 |
|  | DIFF_WC | r | .348 | 1 | .260 | -.110 | .013 | .047 | -.203 | .427 | .439* |
|  |  | p | .122 |  | .255 | .635 | .955 | .839 | .378 | .054 | .047 |
|  | DIFF_FBS | r | .557** | .260 | 1 | -.078 | -.218 | .108 | -.029 | .362 | .378 |
|  |  | p | .009 | .255 |  | .738 | .342 | .641 | .900 | .107 | .091 |
|  | DIFF_TCHOL | r | .017 | -.110 | -.078 | 1 | .628** | -.025 | .870** | .039 | .039 |
|  |  | p | .943 | .635 | .738 |  | .002 | .916 | .000 | .868 | .867 |
|  | DIFF_TG | r | .025 | .013 | -.218 | .628** | 1 | -.306 | .453* | -.064 | -.056 |
|  |  | p | .915 | .955 | .342 | .002 |  | .177 | .039 | .783 | .810 |
|  | DIFF_HDL | r | .080 | .047 | .108 | -.025 | -.306 | 1 | -.126 | .303 | .297 |
|  |  | p | .732 | .839 | .641 | .916 | .177 |  | .587 | .181 | .191 |
|  | DIFF_LDL | r | .030 | -.203 | -.029 | .870** | .453* | -.126 | 1 | .023 | .021 |
|  |  | p | .897 | .378 | .900 | .000 | .039 | .587 |  | .922 | .927 |
|  | DIFF_INS | r | .202 | .427 | .362 | .039 | -.064 | .303 | .023 | 1 | .993** |
|  |  | p | .379 | .054 | .107 | .868 | .783 | .181 | .922 |  | .000 |
|  | DIFF_IR | r | .255 | .439* | .378 | .039 | -.056 | .297 | .021 | .993** | 1 |
|  |  | p | .265 | .047 | .091 | .867 | .810 | .191 | .927 | .000 |  |

**Table 4:** Pearson correlation of differences between the before and after values of Group 2

| Groups | | | DIFF_Myos | DIFF_WC | DIFF_FBS | DIFF_TCHOL | DIFF_TG | DIFF_HDL | DIFF_LDL | DIFF_INS | DIFF_IR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | DIFF_Myosr | | 1 | -.181 | .595** | .624** | .116 | .162 | -.069 | .345 | .348 |
| | | p | | .458 | .007 | .004 | .637 | .508 | .778 | .149 | .145 |
| | DIFF_WC | r | -.181 | 1 | -.278 | -.063 | .181 | .008 | .077 | -.004 | -.008 |
| | | p | .458 | | .249 | .797 | .459 | .973 | .753 | .987 | .973 |
| | DIFF_FBS | r | .595** | -.278 | 1 | .301 | -.064 | -.125 | -.001 | -.046 | -.034 |
| | | p | .007 | .249 | | .211 | .795 | .610 | .997 | .853 | .891 |
| | DIFF_TCH OL | r | .624** | -.063 | .301 | 1 | .120 | .168 | .004 | .025 | .028 |
| | | p | .004 | .797 | .211 | | .625 | .493 | .987 | .921 | .909 |
| | DIFF_TG | r | .116 | .181 | -.064 | .120 | 1 | .093 | -.675** | -.061 | -.049 |
| | | p | .637 | .459 | .795 | .625 | | .705 | .002 | .804 | .842 |
| | DIFF_HDL | r | .162 | .008 | -.125 | .168 | .093 | 1 | -.068 | .321 | .282 |
| | | p | .508 | .973 | .610 | .493 | .705 | | .781 | .180 | .243 |
| | DIFF_LDL | r | -.069 | .077 | -.001 | .004 | -.675** | -.068 | 1 | -.011 | -.007 |
| | | p | .778 | .753 | .997 | .987 | .002 | .781 | | .964 | .978 |
| | DIFF_INS | r | .345 | -.004 | -.046 | .025 | -.061 | .321 | -.011 | 1 | .997** |
| | | p | .149 | .987 | .853 | .921 | .804 | .180 | .964 | | .000 |
| | DIFF_IR | r | .348 | -.008 | -.034 | .028 | -.049 | .282 | -.007 | .997** | 1 |
| | | p | .145 | .973 | .891 | .909 | .842 | .243 | .978 | .000 | |

have found, lower LDL levels in subjects who exercised regularly when compared with those who did not.[13,14] The mechanism of exercise-induced lipid changes is not very clear. Satoru Kodama et al in there meta-analysis found a decrease in HDL-Cholesterol levels after exercise in general but, they found that the Mean differences in HDL-Cholesterol levels was not significant when the duration of exercise was less than 30 minutes per session.[15] Kraus W et al have mentioned in their study the beneficial effect of exercise on the LDL and HDL – C levels increases with increase in intensity of the exercise, however they also mention that LDL is lowered in those individuals who exercise even if it were of moderate intensity than in comparison with sedentary individuals which is consistent in our study.[16]

Insulin levels and Insulin resistance have shown a statistically significant decrease in median values in group 1 subjects after exercise, thus reflecting improved insulin sensitivity.

Keshel TE et al in their review article have described that there was a decreased in insulin resistance with regular exercise even if there was no weight loss. But also suggest that the Insulin resistance reverts back to base line once the exercise is discontinued.[17] Similar finding have been reported in children and adolescents.[18] Insulin is improved as an adaptation to weight loss due to exercise than to decreased caloric intake. Even in those Diabetic women of menopausal age exercise improved Insulin Sensitivity.[19] When adaptations following weight loss are compared between caloric restriction and exercise, improvements in insulin stimulated glucose disposal occur similarly with greater adaptations from exercise-induced weight loss. Additionally, exercise-induced weight loss stimulates mitochondrial oxidative capacity and impacts endogenous glucose production by significantly suppressing unnecessary gluconeogenesis. The efficacy of sustained improvements in glucose metabolism may be influenced by exercise intensity as it relates to changes in body composition.

Insulin resistance describes the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in a normal population. The exact molecular action that leads to insulin resistance is not yet understood. It is well established that acute exercise is associated with substantial improvement in insulin sensitivity. A single bout of moderate intensity exercise can increase the glucose uptake by at least 40%. Several of the early studies observed significant improvements in glucose tolerance and insulin sensitivity in response to exercise training.

Serum Myostatin levels in group 1 has reduced significantly after regular exercise with a P value of <0.001. Expression of Myostatin mRNA in the skeletal muscles of experimental animals has been observed to be significantly reduced following exercise.[20–24] In the experimental animals the low levels of Myostatin is also associated with increased skeletal muscle growth.[25] Myostatin, also known as GDF8 (growth differentiation factor 8), belongs to the transforming growth factor superfamily of secreted growth and differentiation factors. Like other members of TGF family, Myostatin is also produced as a precursor protein composed Arg-X-X-Arg proteolytic cleavage site, an N-terminal pro-peptide region, a signal sequence, and a C terminal domain that dimerizes to

form the active form.[26–28] Follistatin, hSGT, Titin cap and Decorin are proteins found in muscles bind to Myostatin and negatively regulate Myostatin activation, secretion or receptor binding. Myostatin is involved with other ligands acts in tandem to regulate the muscle growth however how the exact mechanism how this is brought about still requires to be illustrated.[28]

When the differences between pre-exercise and post exercise set of values of the variables were compared, Myostatin correlated strongly with waist circumference and fasting blood sugars and weakly with insulin and insulin resistance. (Tables 3 and 4) When the values for Myostatin were independently compared with other variables, it correlated positively with FBS, WC, Insulin levels and Insulin resistance weakly in group 1, before and after exercise and in group 2, before exercise. In group 2, after exercise, the values for Myostatin showed a strong positive correlation with WC, FBS, Insulin levels and insulin resistance.

Myostatin is shown to have multiple cell signaling pathways. It binds to the Activin receptors IA and IIB. It's affinity for IIB is greater. Therefore, it's major effects are seen on binding to the Activin receptor IIB. Further down several secondary signaling cascades are recruited out of which the main cascade that is described is the SMAD 2 and 4 which dimerize and enter the nucleus to regulate transcription. This results in decrease in muscle mass and an increase of adipose content. The exact mechanism is yet to be deciphered. Several mouse model experiments have shown that Myostatin inhibition lead to an increase in muscle mass and a decrease in adipose content.[29] Several factors like Irisin, Follistatin may be involved in such cross talks with the adipose tissue resulting in its decrease.[30] The small decrease in the waist circumference in the group 1 could be attributed to such a complicated interplay of many adipokines and myokines which have an effect on the adipose tissue. In the satellite cells of the muscle which can be activated from their normally quiescent state, Myostatin is found to prevent the cells from progressing from G1 and G2 phases of cell cycle. By up regulating p21 Myostatin, decreases the levels of cyclin dependent kinases Cdk2 and Cdk4 and the retinoblastoma protein.[31] Another study showed that Myostatin down regulates Cdk 4 activity via promotion of degradation of cyclin D1.[32]

Myostatin also has been observed to recruit several other cell signaling molecules such as MAPK, Akt and GSK beta which are antagonistic to the insulin action. Well known is the de -phosphorylation of the Akt which h as an opposing effect to that of insulin. Myostatin knock out in the mice has been subsequently found to increase the expression of the GLUT 1 and the GLUT 4 receptors on the plasma membrane.[32,33] Cell signaling through the MAPK, GSK beta pathways bring about an overall increase in glucose disposal by the muscle tissue. All these mechanisms increase the insulin sensitivity and glucose utilization. Therefore, decreasing glucose levels and increasing insulin sensitivity could be due to a decrease in Myosta tin levels while the strong correlation seen in group 2 between insulin resistance and Myostatin could be as a result of worsening insulin resistance with increasing Myostat in values. In view of all the findings cited in this study, it is obvious Myostatin can be used as a biomarker to measure the compliance to exercise, advised as a life style modification in pre-diabetics. This pilot study can be extended to a larger population to emphasize on the role of serum Myostatin in pre-diabetics.

## 5. Conclusion

The decision to intervene with oral hypoglycemic agents can be deferred, if found non-compliant, by re-affirming the significance of exercise as a simple, physical, non-medicinal, prophylactic approach to prevent florid Diabetes Mellitus. Any drug has it's own set of side effects that become pronounced on long term usage. Hence, intervention that follows a "no drug approach" in any pre-morbid condition, to arrest it's progress to a morbid phase, is always safer and healthier.

## 6. Acknowledgements

## 7. Conflict of interest

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