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Effect of Lifestyle Modification Intervention on Antimetabolic Syndrome Drug Treatment Requirement of patients with Metabolic-Syndrome-Associated-Disorders at University of Nigeria Teaching Hospital Ituku Ozalla, Enugu

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ABSTRACT

BACKGROUND: Lifestyle modification is the process of gradual adaptation of corrective lifestyle habits such as diet, physical activity, and sleep for the prevention and management of various diseases. Metabolic syndrome encompasses disorders underscored by metabolic irregularities. Nearly 25% of the global population is affected by metabolic syndrome-associated disorders (MSADs), which account for most medical outpatient visits and drug prescriptions. As therapeutic adjuncts, lifestyle modification interventions may have a substantial impact on anti-metabolic syndrome drug treatment requirements for control of phenotypic expressions of MSADs. The aim of this study is to determine the combined effect of lifestyle modification on MSADs as therapeutic adjuncts.
MATERIALS AND METHODS: This was a longitudinal study and part of a randomized controlled trial of lifestyle modification intervention for the management of metabolic syndrome-associated disorders approved by the UNTH ethics committee. Collaborating dieticians, medical sociologists, and exercise physiotherapists assigned Lifestyle Modification Scores (LMS) of GOOD=4-5, FAIR=3, and POOR=0-2 to the patients after diet, sleep, and exercise analysis. Anti-metabolic Syndrome Drug Treatment Requirement (ADTR) score was calculated as the total number of defined unitary dosages of anti-metabolic syndrome drugs times adherence +/- 0.1 accordingly for each unitary or decimal increase/decrease from normal values of clinical/laboratory markers of metabolic syndrome-associated disorders.
RESULTS: There was no significant reduction of Actual Drug Treatment (AdhRx) and ADTR scores of study participants with good LMS, although the mean of the scores was lower than that of those with bad LMS ($P > 0.05$).
CONCLUSION: We conclude that ADTR scores are useful and valid tools to assess the impact of lifestyle modification that addresses the aetiopathogenic mechanism in MSADs. This enables differentiation between control of phenotypic expression of MSADs by drugs and that due to lifestyle modification.

1. INTRODUCTION

Metabolic syndrome (MS) has become one of the major public health challenges worldwide. The prevalence of MS varies across different populations[1, 2]. Epidemiological studies have reported the prevalence of MS at about 5–7% in young people worldwide. Older-aged people are more likely to have MS[3, 4]. Varying prevalence of MS has been reported across different populations. In the Philippines, the general population has a prevalence of 18.6%, 19.1% in Uganda, 33.1% and 37.1% in populations across Iran, 29.2% in the Netherlands, and 25% in Canada and Australia, ranging between 21.1% and 30.7%[5]. Lifestyle has an important role in the progression of numerous risk factors of MS. Lifestyle modification could reduce the prevalence of this disease. Persons with MS are frequently overweight and have sedentary behavior[5]. Prolonged screen

time and inadequate physical activity seem to interfere with triglyceride clearance as well as glucose metabolism[6,7].

Diet has a major role in progression of MS. The prevalence of MS was found to be common among subjects who favor omnivores than vegetarian meals (47.55%) in a cross-sectional analysis of 773 subjects. This finding was attributed to the lower levels of glucose and triglycerides in vegetarian diet[8, 9]. A personalized food avoidance dietary approach to stop hypertension (PFADASH) a modification of Dietary Approach to Stop Hypertension (DASH) was conceived to address primary and secondary intolerance to immune unfamiliar and egregious food substances to abate immune dysfunction underlying immune mediated inflammatory diseases like hypertension. Hence its emphasis is on dietary proscription and not prescription (what to avoid and not what to take). Pilot observational studies suggest that not only does a PFADASH address immune dysfunction which begets hypertension, it may also be beneficial for management of a spectrum of immune mediated inflammatory diseases like Metabolic Syndrome Associated Disorders (MSADs)[10,11]. Inadequate sleep is one of MS risk factors. Insufficient sleep can lead to mental and physical stress and increase the incidence of obesity and diabetes. Obstructive sleep decrease the level of High Density Lipoprotein ((HDL), increased level of glucose, body weight, insulin resistance and cardiovascular diseases[12,13].

According to a putative immunotoxiepigenetic disease model for MSADs, diet mediated immune dysfunction initiates the activation and dysfunction of T cells, while other immune dysfunctional states promoted by inadequate sleep and lack of exercise consolidate this dysfunction. Poor diet and inadequate sleep/lack of exercise were considered as initiators and consolidators of immune dysfunction underlying MSADs, respectively[14].

Rational use of anti-metabolic syndrome drugs entails prescription commensurate with the clinical and laboratory parameters of patients. Clinicians usually rely on 'soft' outcome parameters, such as blood pressure, glucose and lipids to match patients with effective drug treatment requirement for MSADs. Measuring not only drug treatment response but also drug requirement, would be helpful in managing and preventing their complications as well as preventing irrational use of drugs (with its attendant health hazards and wastage of limited resources). Rather than relying on only drugs to suppress disease phenotype, the cornerstone of preventive and personalized medicine should be hinged on lifestyle modification.

Lifestyle modification are instituted at borderline diagnosis of MSADs and are rarely used as interventional therapeutic adjuncts. From literature, studies have shown positive effects of good diet, adequate sleep and exercise on MSADs. Moreover, none of these studies have evaluated the combined effect of good diet, adequate sleep and exercise as therapeutic adjuncts for MSAD management. Hence, the aim of this study is to determine the combined effect of lifestyle modification on MSADs as therapeutic adjuncts.

METHODS:

The protocol for randomized controlled clinical trial of lifestyle modification intervention for management of metabolic syndrome associated disorders was approved by the University of Nigeria Teaching Hospital Health Research Ethics Committee (certificate no. NHREC/05/01/2008B-FWA00002458-IRB00002323).

Study Procedure/design:

Study participants are part of clinical studies to improve immune functionality.

Inclusion criteria:

1. Study participant should be managed for an MSAD: hypertension, Diabetes mellitus, dyslipidemia or hyperuricaemia.
2. On any anti-metabolic syndrome drugs: Anti-hypertensive drugs, Anti-diabetic drugs, Anti-dyslipidemic drugs and Anti-Hyperuricemic drugs.
3. Study participants are adults (age above 17 years, not pregnant), sufficiently literate to follow instructions, have freely given full consent, and undertake their normal daily activities and attend the outpatient clinic without difficulty.
4. Subjects are adults, male or female (not pregnant) i.e. age 18 years and above.
5. Subjects are sufficiently literate to follow instructions, both verbal and on printed sheets (and, if need be, by email or text message).
6. Subjects have freely given full informed consent.

Exclusion criteria

1. Subjects with serious i.e. disabling complications from their chronic disease. This means that they are unable to undertake their normal daily activities and attend the outpatient clinic without difficulty.
2. Patients' who's MSAD is secondary to a treatable underlying cause. Examples include drug-induced

hypertension, hyperaldosteronism, renal artery stenosis, phaeochromocytoma.

3. Pregnancy Exclusion
4. Disabling complications of MSADs late stage kidney disease, sickle cell disease, history of heart attack, stroke, TIA, heart failure

Study participants undertook bi-weekly diet, sleep, exercise and anti-metabolic syndrome drug treatment requirement updates/scoring assessments by collaborating physicians and pharmacists who evaluate anti-metabolic syndrome drug treatments of the study participants.

Diet assessments entailed prospective dietary compliance monitoring and scoring of dietary exposures of study participants as per dietary guidelines.

Sleep assessments entailed evaluation of sleep habits and determination of Sleep Deprivation Index (SDI).

Exercise assessments entailed evaluation of exercise habits with international physical activity questionnaire.

Method for Dietary Assessment

Dietary assessments were done in line with a Personalized Food Avoidance Dietary Approach to Stop Hypertension.

For the PFADASH intervention, Dietary Compliance scoring was based on exposure to:

Primary culprits: amphiphilic fats and oils, glutamatergic flavour enhancers, non-sugar sweeteners

Secondary (facultative) culprits [early life – unfamiliar, food dislikes, autacoids, modest flavourant or sweetener content, preservatives, unduly frequent/ high dose consumption of normally well tolerated foods]

GOOD dietary compliance means that there is established MAJOR (category A) dietary indiscretion less than once a month [OR minor (category B) indiscretion less than once a fortnight]. POOR dietary compliance means that there is established MAJOR dietary indiscretion once a month or more frequently [OR minor indiscretion once a fortnight or more frequently].

Method for Sleep Assessment

Study participants tracked and kept records of their sleep patterns with sleep trackers and personal sleep record booklets. A medical sociologist determined the Sleep Deprivation Index (SDI) scores of study participant biweekly after face to face meetings and perusal of SPs sleep record booklets. An SDI of 0 indicate greater than 8 hours sleep per night (GOOD sleep habit), an SDI of 1 indicate 6 to 8 hours sleep per night (FAIR sleep habit) and an SDI of 2 indicate less than 6 hours sleep per night (POOR sleep habit).

Method for Exercise Assessment

Bi-weekly usual exercise habits of the SPs were evaluated by a physiotherapist using the international physical assessment questionnaire to assess their usual exercise habits and their level of physical activities.

Questionnaire based assessment of usual exercise habits was cross validated by quarterly maximal exercise tolerance assessment on a treadmill as regards the following indices: Max oxygen consumption (VO2 max [ml/kg/min]) and Exercise metabolic equivalent (Kcal/kg/hr.)

Method for deriving Lifestyle Modification Scores

Collaborating dieticians, medical sociologists and physiotherapists evaluate and assign Lifestyle Modification Scores (LMS) for dietary compliance, sleep and exercise habits of SPs.

A Lifestyle Modification Score of 0 - 5 was assigned to an SP based on dietary compliance to a Personalized Food Avoidance Dietary Approach to Stop Hypertension/ sleep/exercise habits. 3 points was allotted to dietary compliance and 1 score to sleep and exercise habits of the SPs.

Good, Fair and Poor dietary compliance to a PFADASH is scored 3, 2 and 1 respectively. A score of 1 was assigned to 0 Sleep Deprivation Index and a score of 1 is assigned to moderate/high physical activity.

A LMS of GOOD=4-5, FAIR=3 or POOR=0-2 is assigned to an SP after totaling the LMS of the SPs following PFADASH, sleep and exercise assessments.

Definitions of unitary dosages of anti-metabolic syndrome drugs

Unitary doses of antihypertensive drugs is defined as follows: Hydrochlorothiazide 25 mg, Amlodipine 5 mg, Atenolol 25 mg, prazosin 1 mg, Lisinopril 5 mg, Enalapril 5 mg, Ramipril 2.5 mg, Losartan 25 mg, Telmisartan 20 mg, Frusemide 20 mg, Methyldopa 250 mg, Valsartan 80 mg.

Unitary doses of anti-diabetic drugs is defined as follows: Metformin 500 mg, Gilbenclamide 5 mg, Repaglinide 2 mg, Rosiglitazone 4 mg, Acarbose 25 mg, Sitagliptin 100 mg, 0.4 units/kg/day of insulin.

Unitary doses of anti-lipidemic drugs is defined as follows: Artovastatin 20 mg, Simvastatin 20 mg, Rosuvastatin 20 mg, Pravastatin 40 mg.

A unitary dose of anti-uricaemic drugs is defined as follows: Allopurinol 300 mg, Febuxostat 40 mg.

Assessment of anti-metabolic syndrome adherence score

Anti-metabolic syndrome adherence score was assessed as follows: No of days of prescribed anti-metabolic syndrome drug divided by number of days it is taken (Adh score).

Assessment of actual anti-metabolic syndrome drug treatment score:

Actual anti-metabolic syndrome drug treatment score was determined by multiplying adherence score (Adh score) by number of the prescribed unitary daily doses (R_x) to give actual anti-metabolic syndrome drug treatments scores ($AdhR_x$scores).

Assessment of anti-metabolic syndrome Drug Treatment Requirement score (DTR score)

For antihypertensive DTR, add 0.1 to AdhRx score for each unitary rise in mmHg that average systolic Automated Office Blood Pressure reading exceeds 120 mmHg (subtract 0.1 from AdhRx score for each unitary mmHg that average systolic AOBP fall lower than 120 mmHg)

For anti-diabetic DTR, add 0.1 to AdhRx score for each unitary rise in mg/dl that fasting blood sugar level exceeds 120 mg/dl (Subtract 0.1 from AdhRx score for each unitary mg/dl that fasting blood sugar fall lower than 120 mg/dl)

For anti-lipidemic DTR, add 0.1 to AdhRx score for each unitary/decimal rise in ratio that HDL: LDL ratio exceed 3.5:1 respectively (subtract 0.1 for each unitary/decimal fall in ratio that HDL: LDL ratio fall lower than 3.5:1 respectively)

For anti-uricemic DTR, Add 0.1 to AdhRx score for each rise in mg/dl that serum uric acid level exceeds 8.5 mg/dl (subtract 0.1 for each unit decrease in mg/dl that serum uric acid level fall lower than 4.0mg/dl)

A sum of respective DTRs for anti-hypertensives, anti-diabetics, anti-lipidemics and anti-uricemics gives anti-metabolic syndrome drug treatment requirement score.

Frequency of drug doses were determined by attending physicians based on assessed clinical and laboratory markers of MSADs.

Data was analyzed using Statistical Package for Social Sciences version 25 and Microsoft Excel.

Longitudinal trend analysis of AdhRx and ADTR scores for graph analysis was done with Corel Draw Microsoft software.

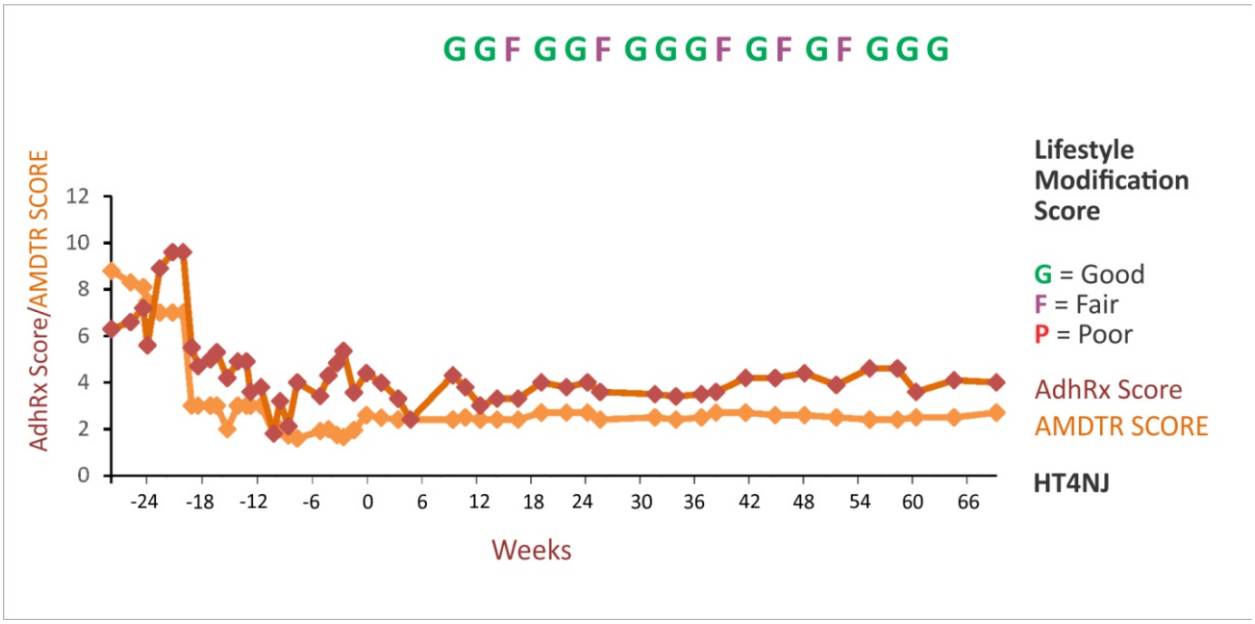
RESULTS

Table 1: Comparison of Actual Drug Treatment scores between study participants with Good and Fair/Poor LMS

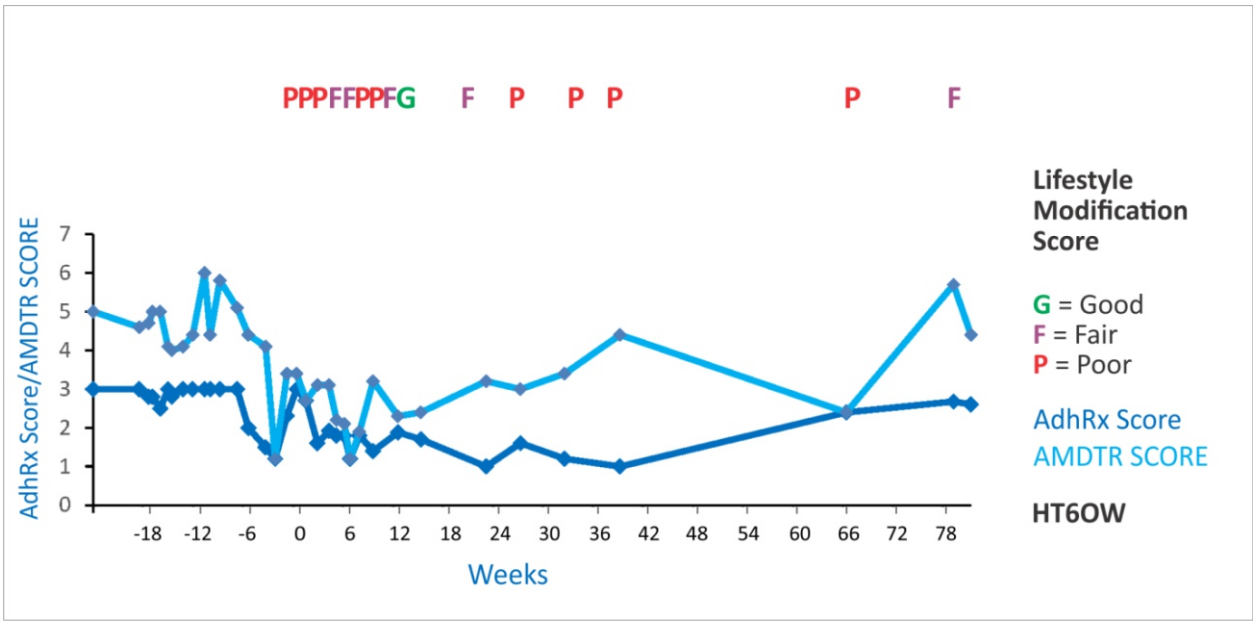
Time points	Good LMS	Poor LMS	p - value
Timepoint 5	3.56 ± 2.14	4.00 ± 0.88	0 .756
Timepoint 6	4.17 ± 2.29	4.20 ± 0.84	0 .976
Timepoint 7	4.55 ± 3.93	4.13 ± 1.18	0 .836
Timepoint 8	3.79 ± 1.89	4.27 ± 1.60	0 .713
Timepoint 9	2.68 ± 1.17	4.48 ± 1.28	0 .081
Timepoint 10	2.77 ± 0.32	3.93 ± 1.28	0 .274
Timepoint 11	3.60 ± 1.59	3.09 ± 1.97	0 .710
Timepoint 12	2.80 ± 1.06	3.33 ± 1.69	0 .667
Timepoint 13	3.09 ± 1.52	3.74 ± 1.64	0 .645
Timepoint 14	3.15 ± 1.06	3.74 ± 1.58	0 .668
Timepoint 15	3.20 ± 1.13	4.63 ± 0.48	0 .079
Timepoint 16	3.85 ± 1.63	5.65 ± 4.94	0 .658
Timepoint 17	3.85 ± 1.63	5.33 ± 0.58	0 .220
Timepoint 18	3.85 ± 1.15	4.03 ± 1.63	0 .881
Timepoint 19	2.47 ± 0.09	3.00 ± 2.55	0 .794
Timepoint 26	2.50 ± 0.14	4.53 ± 0.67	0 .053

Table 2: Comparison of ADTR score between study participants with Good and Fair/Poor LMS

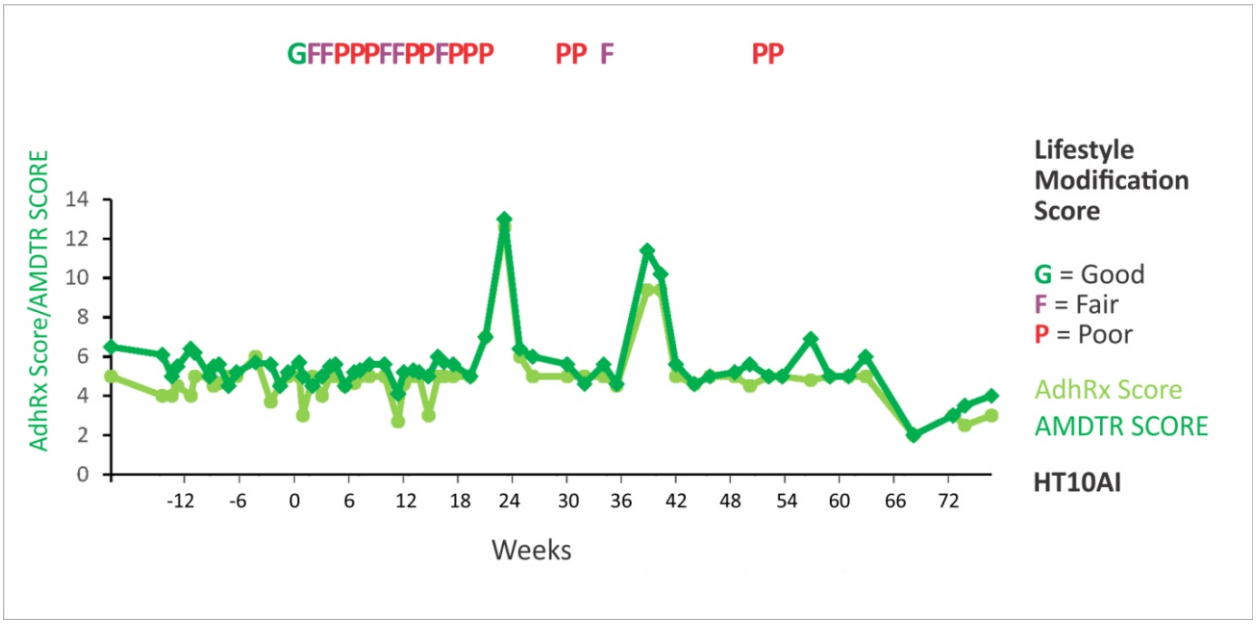
Time points	Good LMS	Poor LMS	p-value
Timepoint 5	5.43 ± 1.08	6.08 ± 1.44	0.634
Timepoint 6	5.54 ± 2.35	5.89 ± 1.21	0.765
Timepoint 7	3.27 ± 0.23	5.51 ± 2.54	0.292
Timepoint 8	5.16 ± 1.27	5.14 ± 1.84	0.987
Timepoint 9	4.54 ± 1.68	5.78 ± 2.03	0.412
Timepoint 10	4.00 ± 0.28	4.81 ± 1.32	0.444
Timepoint 11	5.65 ± 3.28	4.03 ± 1.59	0.333
Timepoint 12	3.67 ± 1.14	4.41 ± 1.04	0.454
Timepoint 13	3.76 ± 1.64	4.50 ± 1.89	0.636
Timepoint 14	3.97 ± 1.38	4.27 ± 1.23	0.802
Timepoint 15	4.80 ± 2.12	4.93 ± 0.94	0.919
Timepoint 16	5.03 ± 1.45	6.55 ± 4.38	0.672
Timepoint 18	8.53 ± 2.58	5.25 ± 1.85	0.140
Timepoint 19	5.02 ± 2.00	4.10 ± 0.99	0.621
Timepoint 26	3.90 ± 0.71	5.58 ± 2.02	0.383



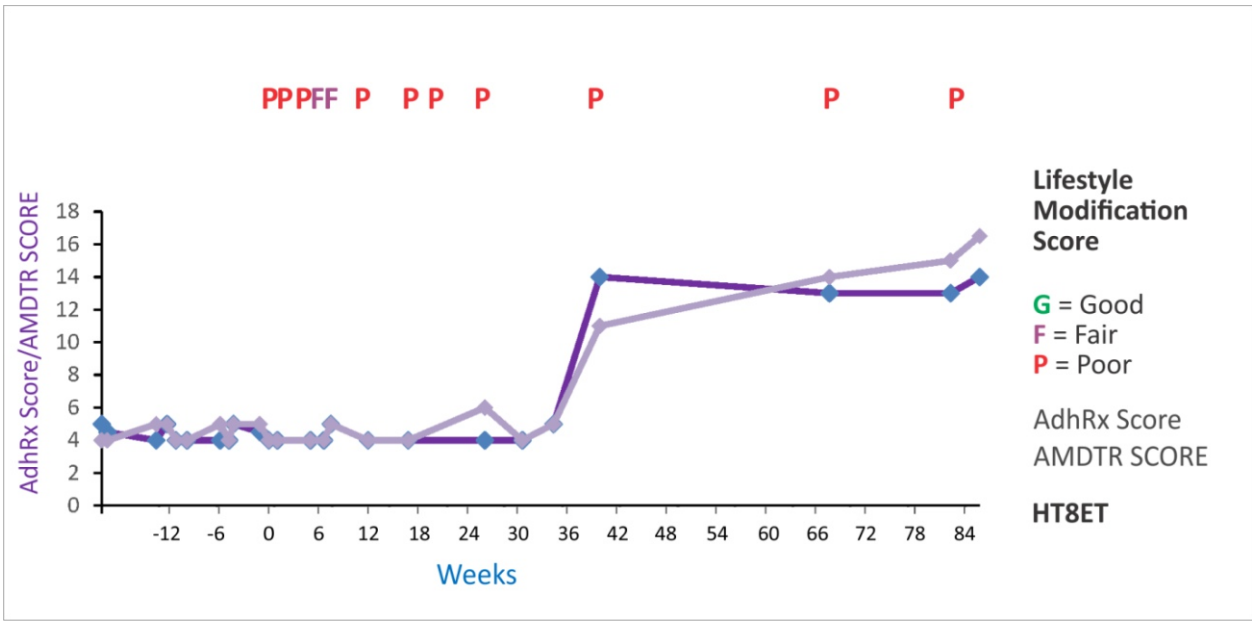
Graph 1: Anti-metabolic drug treatment requirement and actual drug treatment for study participant HT4NJ.



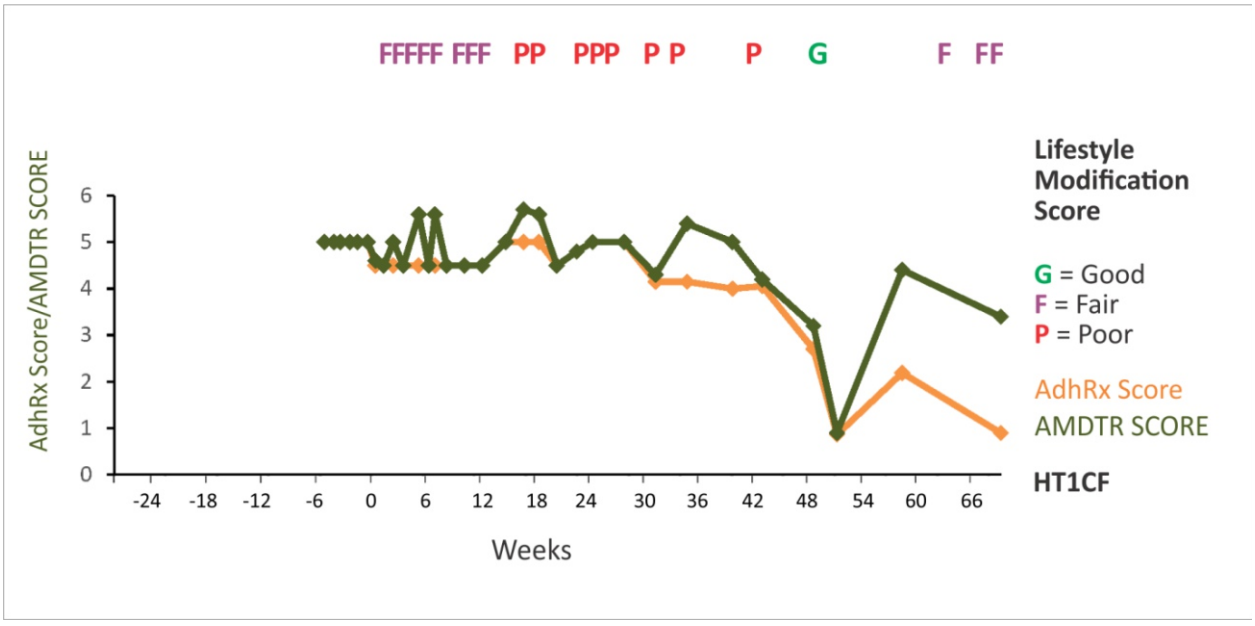
Graph 2: Anti-metabolic drug treatment requirement and actual drug treatment for study participant HT6OW.



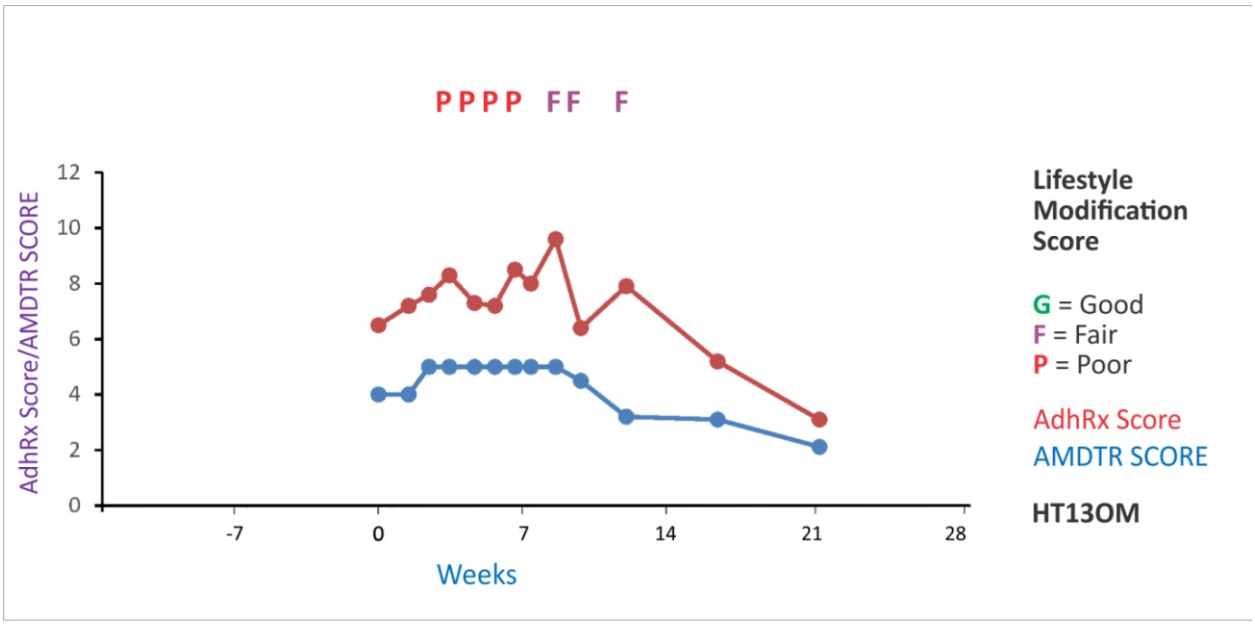
Graph 3: Anti-metabolic drug treatment requirement and actual drug treatment for study participant HT10AI.



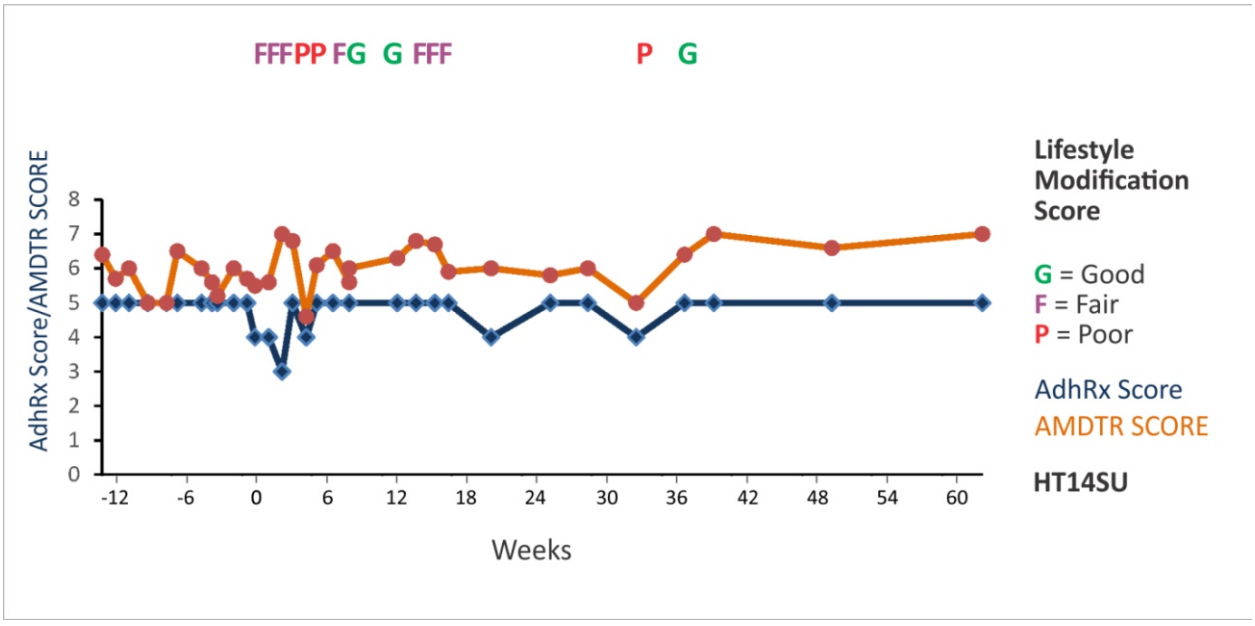
Graph 4: Anti-metabolic drug treatment requirement and actual drug treatment for study participant HT8ET.



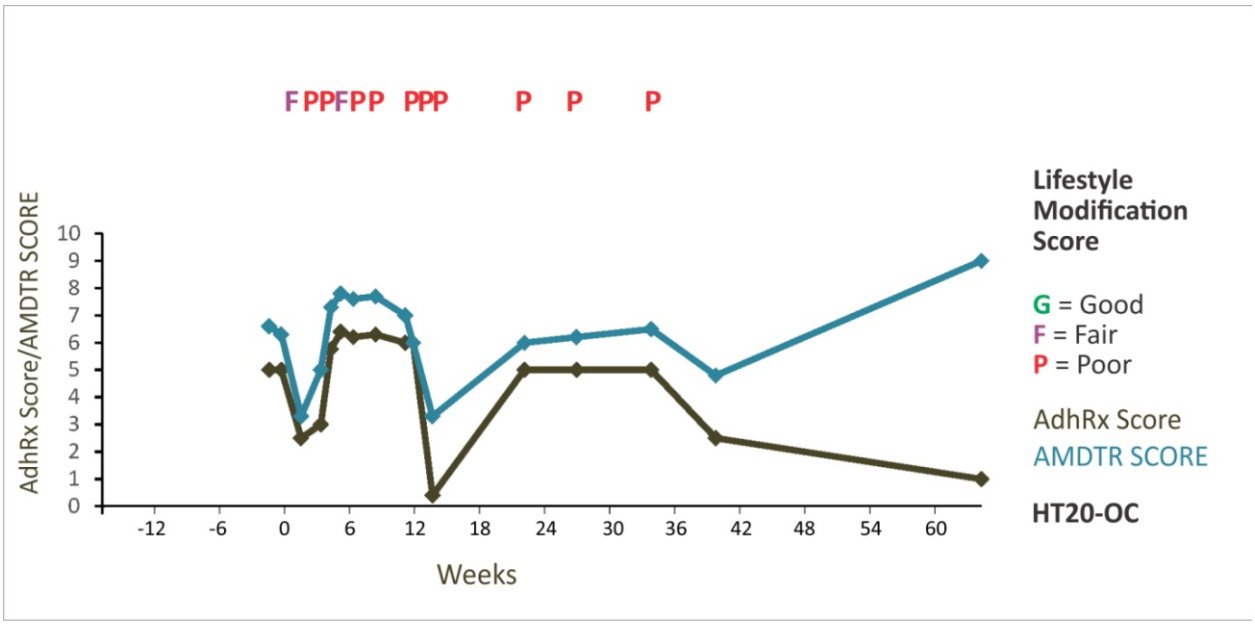
Graph 5: Anti-metabolic drug treatment requirement and actual drug treatment for study participant HT1CF.



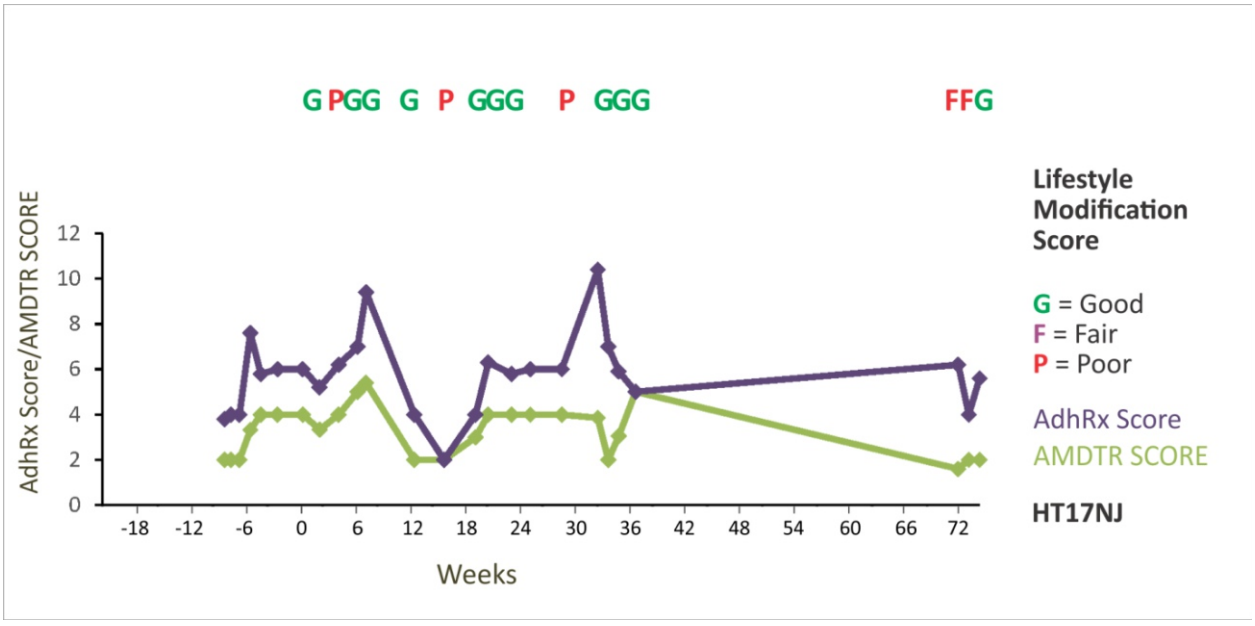
Graph 6: Anti-metabolic drug treatment requirement and actual drug treatment for study participant HT13OM.



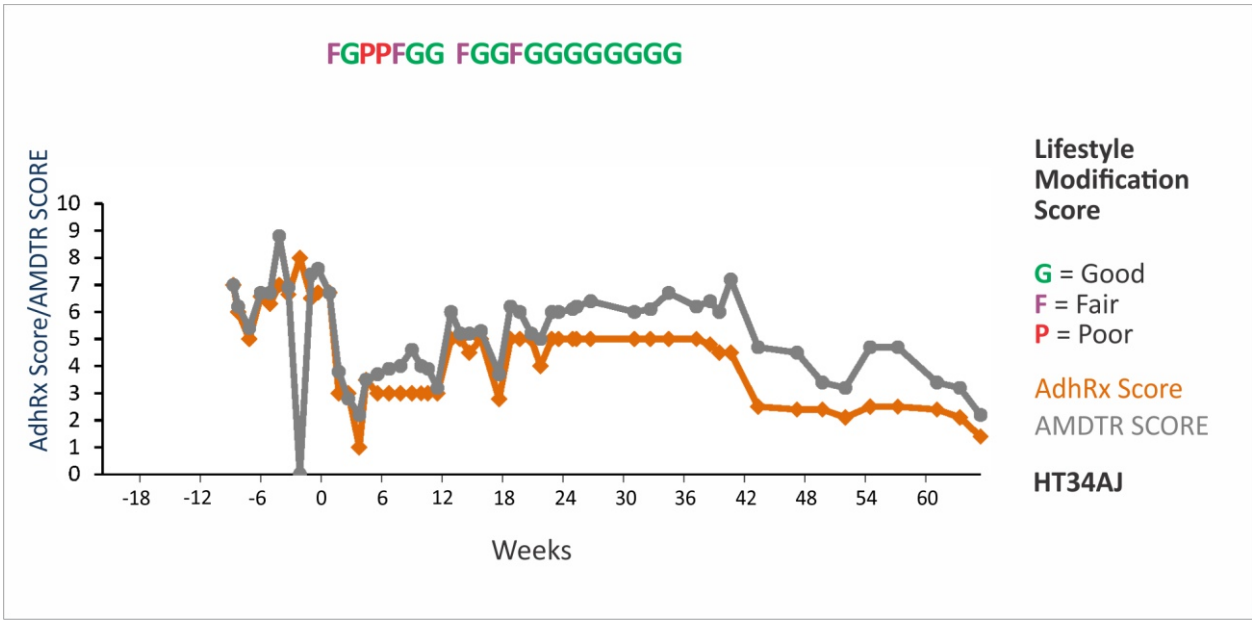
Graph 7: Anti-metabolic drug treatment requirement and actual drug treatment for study participant HT14SU.



Graph 8: Anti-metabolic drug treatment requirement and actual drug treatment for study participant HT20-OC.



Graph 9: Anti-metabolic drug treatment requirement and actual drug treatment for study participant HT17NJ.



Graph 10: Anti-metabolic drug treatment requirement and actual drug treatment for study participant HT34AJ.

DISCUSSION

Phenotype-suppression therapeutics in modern medicine lays emphasis on "what to take" for the management of non-communicable diseases, rather than "what to avoid". There is strong advocating of reversal of this emphasis in therapeutics by addressing the immunotoxi-epigenetic mechanisms of 'metabolic syndrome' – associated immune dysfunction, which not only begets the chronic disease process, but undoubtedly interferes with immunocompetence versus infectious disease challenges as well as neoplastic cell transformation. A new era of therapeutics should be directed at the aetiopathogenesis of human disease, rather than over-reliance on phenotype-suppression strategies, for which the efficacy is, all too often, unreliable in the long term. Lifestyle modification as therapeutic adjuncts could also reduce drug treatment requirements, consequent drug side effects and reduced drug resistance in drug treatment of infectious diseases[15,16].

For ethical reasons, study participants were kept on whatever anti-metabolic syndrome drug treatment they required, while they embarked on adjunctive lifestyle modification immune optimizing interventions. This would reduce utility of clinical and laboratory markers of MSADs as outcome parameters, since control of clinical and laboratory markers of MSADs may be good on drug treatment ab-initio, while later on, control of clinical/laboratory MSAD markers remain good on adjunctive lifestyle modification immune optimization interventions. Hence, anti-metabolic syndrome drug treatment requirement (ADTR) was evaluated in this study as an outcome parameter.

Trend analysis of study participants with good LMS (table 2) show a significant trend decrease in ADTR for HT4NJ and HT34AJ respectively. For those with poor LMS, there was a significant trend decrease in ADTR for study participants HT6OW and HT1CF. There was no significant difference between those with good and poor LMS as regards their ADTR at different time points. The ADTR was almost the same in both groups.

It is important to note that study participants with fair LMS were considered and analyzed as poor LMS. In so doing, only 3 study participants had good LMS and were compared with 7 study participants with fair/poor LMS. This could have decreased the chance of having a significant difference between the two groups. Drug treatment requirements in hypertensive study participants have been shown to decrease after lifestyle modifications[17, 18,11].

Graphs 1-10 reflect trend of ADTR and AdhRx drug treatment scores of SPs with GOOD, FAIR or POOR LMS.

Even with good LMS, we expected a delay of a few weeks to a few months for full reversibility of immunotoxiepigenetic mechanisms to become apparent. The trend of the graphs show occasional overlap of ADTR and AdhRx especially in study participants with good LMS. Such overlaps may infer rational use of drugs [actual drug treatment (AdhRx) equals drug treatment requirements (ADTR)]. Graph trends depicting drug treatment scores could be useful in therapeutics as regards gauging the effect of lifestyle modification intervention over a period of time as well as determining overlaps between drug treatment scores.

Rational use of anti-metabolic syndrome drugs entails prescriptions and proscriptions commensurate with the clinical and laboratory parameters of patients. Clinicians often rely on 'soft' outcome parameters, such as blood pressure, blood glucose and blood lipids to match patients with effective drug treatment requirement for MSADs. Measuring not only drug treatment response but also drug requirement, would be helpful in managing and preventing their complications as well as preventing irrational use of drugs (with its attendant health hazards and wastage of limited resources). Rather than relying on only drugs to suppress disease phenotype, the cornerstone of preventive and personalized medicine should be hinged on immune optimization via lifestyle modification.

Anti-metabolic syndrome drug treatment requirement and adherence scores (ADTR and AdhRx scores) were extracted from study participants for different time points to ascertain drug treatment distribution scores. For AdhRX and ADTR scores all sets of data were normally distributed. Both scores showed more than 75% likelihood of being normally distributed at 5% significance level (i.e. 12 out of 16 data sets tested).

Study Limitation

Drug metabolites in urine samples of study participants was not assayed at different time intervals to cross validate and correlate ADTR scores due to financial constraints. Also, the study did not consider the impact of demographics of the study participants with their drug treatment scores.

CONCLUSION

Our study has shown that lifestyle modification interventions may serve as therapeutic adjuncts for the management of Metabolic Syndrome Associated Disorders. However, it should not eschew drug treatment whose requirement may be reduced as well as side its effects.

Author's contributions

This manuscript has been read and approved by all the authors for the publication. The requirements for authorship were met as outlined below.

CPC: Concept, design, intellectual content, literature search, methodology. MTO: Intellectual content, literature search, article screening and manuscript preparation. IC: Literature search, article screening. AUM: Statistical analysis. RCA: Literature search, manuscript review and Design AQU: Article screening and manuscript review.

Ethical approval

The protocol for the randomized controlled trial of personalized food avoidance dietary approach to address hypertension was approved by the University of Nigeria Teaching Hospital Ethics Committee (certificate number. NHREC/05/01/2008B-FWA00002458-IRB00002323)

Informed consent

All study participants consented to the study.

Availability of Research data

Available on request to the corresponding author

Declaration of Helsinki

We declare that the study was conducted in accordance with the principles of Helsinki declaration.

Financial support and sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.

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