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Rapid effects of novel phytoandrogen adjuvant therapy (PAT) on metabolic health: a gender, age and BMI matched case-control study

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Abstract

Background and Aim: The human androgen receptor (AR) is a key nuclear transcription factor that controls expression of genes involved in anabolism - such as musculoskeletal remodelling and body fat mobilisation to ATP energy production – processes which directly impact aspects of metabolic health. This study evaluates the adjuvant effects of orally administered AR-modulating phytoandrogens and suprahormonal lipidic augmenters (SuHLAs) combined with an integrative weight-healthcare regimen of polyvalent pharmacotherapy (hypoglycemic, lipid modifying and anti-inflammatory) and mild lifestyle intervention, over intervals of 2-4 weeks.

Method: The total intention-to-treat (ITT) population consisted solely of women (N = 15) and were screened at baseline for metabolic health status, assessed via arterial blood pressure (BP), body fat (BF), lean muscle mass (LMM), body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR). This gender matched ITT population were then stratified into two treatment groups that were age and BMI matched: 1) patients opting for a metabolic health program (control group, n = 5, mean BMI = 26.6 kg/m^2, mean age = 45 years), and 2) patients treated with a metabolic health program plus phytoandrogen adjuvant therapy (PAT group, n=10, mean BMI = 26.5 kg/m^2, mean age = 44 years).

Results: After treatments averaging 2.8 weeks (control group) and 2.9 weeks (PAT group), mean systolic and diastolic BPs in the total ITT population were lowered by 5 mmHg and 4 mmHg respectively, from 116/79 ±4 mmHg to 111/74 ±2 mmHg (P =0.05). Mean BF showed negligible loss of 0.2% (P >0.05) in the control group, in contrast to a highly significant reduction of 0.8% in the PAT group (P <0.001). Muscle mass in the PAT group was protected from atrophy (±0 kg change in LMM, P >0.1). Both treatment groups showed comparable improvement in BMI, WC and WHR. The control group had mean reductions of -0.25 kg/m^2 (BMI, P <0.05), -2 cm (WC, P <0.05) and -0.03 (WHR, P<0.05), while the PAT group showed reductions of -0.35 kg/m^2 (BMI, P =0.01), -3 cm (WC, P =0.01) and -0.03 (WHR, P =0.01). Measured against the top WHR bracket, odds ratios (ORs) for WHR-associated risk for diabetes, hypertension or dyslipidemia (WHR ≥0.9, OR 5.4) in the control and PAT groups were lower by 19% (WHR =0.88 ±0.02, OR 4.38) and 48% (WHR =0.83 ±0.01, OR 2.81) respectively.

Conclusion: Oral phytoandrogenic SuHLAs therapy can rapidly potentiate aspects of AR-mediated anabolism within a low intensity metabolic health program. Secondarily, in contrast to physiological androgens and anabolic steroids, phytoandrogenic modulators of the AR in this study did not aggravate arterial tension. This is the first case-control report on the pharmacologic use of true phytoandrogens (cognate ligands of the AR) and SuHLAs to aid metabolic competency.

Keywords: Phytoandrogen adjuvant therapy; Lifestyle intervention; Metabolic health; Androgen receptor; Suprahormonal lipidic augmenters; Sarcopenic obesity; Adiposity

Introduction

The metabolic syndrome (MetS) is characterised by impaired glucose tolerance, adiposity, central obesity, chronic inflammation and vascular resistance. Sequelae of the MetS include stroke, heart disease, fatty liver disease, overt diabetes and types of cancer. Central to these disparate clinical presentations of metabolic dysfunction is bio-energetics i.e. energy flux (total caloric intake versus energy expenditure), energy distribution (glycogen, fat and protein stores) and energy metabolism (gluconeogenesis, glycolysis, lipogenesis, lipolysis, tricarboxylic acid cycle etc).

Androgen receptor (AR) mediated anabolism, such as musculoskeletal growth and AR mediated catabolism that influences fat mobilisation are intricately cross-linked to bio-energetics, and could benefit clinical management of the MetS [1-3]. The wild-type (normal) AR requires the cognate binding of an androgen to its ligand binding domain (LBD) to be transcriptionally active. In turn, the transcription of AR-responsive genes lead to downstream messenger RNA translation and a cascade of metabolic events that ultimately impact aspects of systemic growth, remodelling and maintenance, including the musculoskeletal, hematopoietic, neurologic, cardiovascular and reproductive system [4-7] (Figure 1).

However, androgen pharmacotherapy with testosterone, dihydrotestosterone (DHT) and anabolic steroids carries many limitations, such as the requirement for parenteral or transdermal formulations, and severe side effects that include hypertension and hyperandrogenism (such as amenorrhea, insulin resistance, hirsutism and acne). As such, development of orally bioavailable agents that can modulate the AR, without the limitations associated with androgen replacement therapy, is critical in enabling AR-mediated clinical benefits to be safely translated from the molecular level to the medicinal level.

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To this end, triterpene phytoandrogens isolated from *Eucommia ulmoides* have been reported to act as novel modulators of the AR, by competitively displacing testosterone from the ligand binding domain (LBD) of the AR [8,9]. Upon cognate AR-LBD binding, these true phytoandrogens then act as weak agonists, with phytoandrogen-liganded AR having transactivational capacity (activation of gene expression) of less than 10% relative to DHT-liganded AR; the latter being the strongest physiological agonist of human AR activity.

Separately, suprahormonal lipidic augmenters (SuHLAs) interact synergistically with the AR and its cognate ligands (phytoandrogens or androgens) to double AR-driven gene expression. Together, cognate (true) phytoandrogens and SuHLAs represent a more selective means of controlling/calibrating AR-mediated anabolism.

Previously, a novel polyvalent medicine-augmented lifestyle program lasting 7-13 months have been reported to reverse metabolic dysfunction (case reports, N = 4), evaluated using fasting blood glucose, arterial blood pressure, lipid profile (HDL-C, LDL-C, total cholesterols and triglycerides) and atherosclerotic index (HDL-C/TC) [10]. Of these, two case studies included phytoandrogen adjuvant therapy (PAT). Here, we present a larger case-control study that is gender, age and BMI matched (N = 15), which examines the rapid effects of the program (n = 5) alone, and in combination, with PAT (n = 10).

Methodology

Female patients for this case-control study (N = 15) that are matched in age and BMI, were enrolled into an integrative weight-healthcare program with mutual consent. Cohort data is stratified into two groups – women that underwent polyvalent pharmacotherapy-augmented lifestyle intervention (control group, n = 5, mean age = 45 years, mean BMI = 26.6 kg/m^2) and women that were received a combination of phytoandrogen adjuvant therapy (PAT) and polyvalent pharmacotherapy-augmented lifestyle intervention (PAT group, n = 10, mean age = 44 years, mean BMI = 26.5 kg/m^2).

Treatment intervals for individual patients ranged from 2 to 4 weeks, with the control and PAT groups averaging 2.8 weeks and 2.9 weeks respectively. The augmented lifestyle intervention method and overarching model have been described previously [11].

Briefly, the minimalist regimen comprised of dietary protein and lyophilised vegetable supplements, with daily strolling (gentle walk) of 30-45 min duration. The stroll took the forms of either – a) slow pacing at home, b) treadmill use at set speed of 2 km/hr, or c) outdoor leisure walking (no jogging or brisk walking). Apart from reducing the risk of joint injury, the low intensity exercise also helps to improve patient compliance with regard to daily physical activity; levelling out any variability in metabolic response due to the latter during the course of adjuvant therapy.

Behaviorietary use of non-caloric table sweetener and naturally flavored drinks was *ad libitum*; conversely, use of alcohol and salad dressings was discouraged. Dietary changes also included partial substitutions of red meat and seafood intake, with non-fried white meat and fish, whilst daily consumption of leafy greens was encouraged.

Metabolic health in patients were assessed via blood pressure (BP), waist-to-hip ratio (WHR), waist circumference (WC), body fat (BF) and lean muscle mass (LMM).

BP readings (at least 30 min of rest in seated position) were taken from the left brachial artery using digital blood pressure monitor with automated inflatable upper arm cuff (Omron Corp, Japan), validated by the European Society of Hypertension (ESH), British Hypertension Society (BHS) and the Association for the Advancement of Medical Instruments (AAMI).

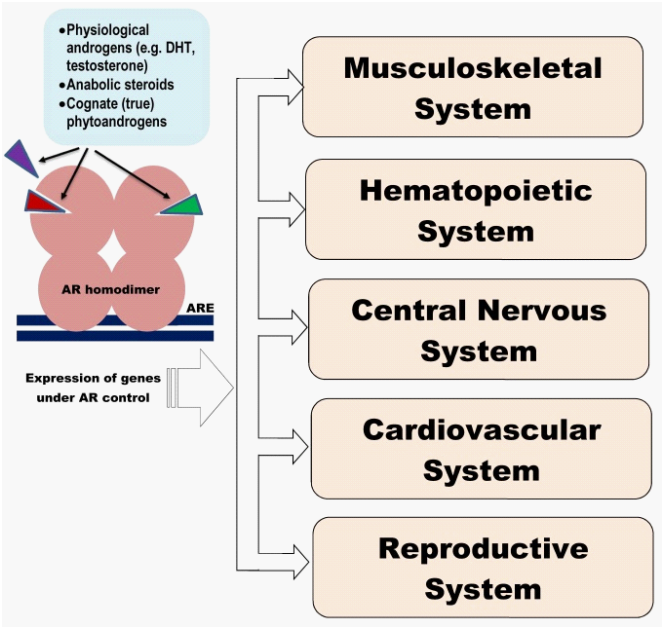

Figure 1: Schema of the androgen receptor (AR) in transcriptionally active dimer formation, with bound (cognate) ligands, interacting with androgen response elements (ARE) of anabolic genes, culminating in systemic effects on bodily structure and function.

BF and LMM measurements were conducted using bio-impedance (BIA) body composition analyser (Tanita Corp, Japan), United States FDA compliant. Waist and hip circumference readings were carried out with an anthropometric tape measure. Height measurements were taken to the nearest mm with a floor stadiometer (Seca, Germany).

Waist measurements to the nearest 0.5 cm were conducted midway between the lower rib margin and the iliac crest, with the umbilicus as the anterior landmark. Hip measurements were taken over the great trochanters to the nearest 0.5 cm; anterior and posterior landmarks were the lower hypogastrium (mons pubis) and prominence of the gluteus maximus (nates) respectively [12].

The polyvalent medicine (ES-Triguard) augmenting lifestyle intervention in this study, which targets peroxisome proliferator-activated receptors (PPARs), Na^+-coupled glucose transporters (SGLT), facilitative glucose transporters (GLUT), gastrointestinal disaccharidases, lipases and inflammation, is listed in the Monthly Index of Medical Specialities (MIMS), and regulated under the Medicines Act (Annex II, Quasi Medicines).

Phytoandrogens and SuHLAs for PAT were delivered via a proprietary oral formulation (Enerbolis), regulated under the Medicines Act (Annex I, Health Supplements). *E. ulmoides*-derived phytoandrogens and SuHLAs used in this study have previously undergone *in vivo* pharmacological and toxicological studies in animals (N = 24), which established oral bioavailability; and importantly, the absence of toxicity (highest tested dosage equivalent to an adult human with body weight of 70 kg, ingesting 17.5 g of proprietary extract once daily), with no observed mortality nor end-organ damage. Laboratory autopsy on sacrificed animals at end-of-study was carried out by the Agri-Food and Veterinary Authority (AVA) of Singapore [13].

Results

Both control and PAT treatment arms showed improvements in their metabolic health, evaluated with BP, BMI, BF, WHR, WC and LMM, over the course of 2.8 and 2.9 weeks respectively (Table 1).

The systolic pressure of the total ITT population (N =15) was lowered significantly by 5 mmHg (P =0.05), from 116 ±4 mmHg to 111 ±4 mmHg. Concomitantly, diastolic pressure was lowered significantly by 4 mmHg (P =0.05), from 79 ±2 mmHg to 74 ±2 mmHg (Figure 2).

Analysed separately, the mean BP in the control group (n =5) at baseline (visit 0) was 115/79 mmHg. After polyvalent medicine-augmented lifestyle intervention, the mean BP was 109/76 mmHg. The mean differences, while not statistically significant (P >0.1), were -6 mmHg (systolic) and -3 mmHg (diastolic) respectively. Similarly, in the PAT group (n =10), mean BP readings at baseline and post-treatment were 116/79 mmHg and 112/75 mmHg respectively. Due to the lower power when divided into separate treatment arms, the mean systolic and diastolic changes for the PAT group were not statistically significant, at -4 mmHg (P >0.05) and -4 mmHg (P >0.1) respectively.

After 2-4 weeks of treatment, the body mass of control and PAT groups showed small reductions, with BMI differentials of -0.25 kg/m^2 (P <0.05) and -0.35 kg/m^2 (P =0.01) respectively. Statistically significant changes to body morphology were measured; WHR values improved in both treatment groups by the same margin of -0.03 (P <0.05, control group; P =0.01, PAT group), while improvements in WC were -2 cm (P <0.05, control group) and -3 cm (P =0.01, PAT group). While the control and PAT groups had comparable magnitude of improvement to their mean BP, BMI, WC and WHR values, the specific metabolic processes (fat lysis and protein synthesis) impacted directly by AR endocrine control showed marked differences. The negligible BF loss was -0.2% (P >0.05) in the control group in contrast to a highly significant 4-fold reduction in the BF of the PAT group at -0.8% (P <0.001).

Concurrently, the LMM of the PAT group was protected from atrophy (0 kg loss between visit 0 and visit 1, P >0.1 i.e. null hypothesis of change in LMM between visits is valid), compared to the control group, which experienced a borderline reduction in muscle mass (0.2 kg loss between visit 0 and visit 1, P >0.05).

Discussion

In this study, we examine the effects of phytoandrogen adjuvant therapy (PAT) in combination with a minimalist model of lifestyle intervention; the latter having been reported to reverse metabolic dysfunction and stabilise the MetS [10,14]. This intervention model modulates not only energy flux (typically targeted through calorie restriction and/or significantly increased physical activity), but also, energy distribution (such as reducing fat mass and improving muscle mass) and energy metabolism (PPAR-mediated lipid changes, AR-mediated anabolic changes, GLUT/SGLT-mediated glucose transport, reducing insulin resistance etc).

The results of this study provide further clinical evidence that through energy tri-modulation (flux, distribution and metabolism), aspects of metabolic health can be improved, without relying on restrictive dieting and/or brisk exercise. For instance, the low intensity lifestyle changes in this study already conferred a minor but significant weight reduction effect within 2-4 weeks, with control and PAT groups showing declines in BMI of 0.25 kg/m^2 (P<0.05) and 0.35 kg/m^2 (P=0.01) respectively (Table 1).

More importantly, improvements in morphological endpoints (WC and WHR) of the control group vis-à-vis the PAT group were clinically relevant with respect to risk reduction. The WC measurements in the control and PAT groups narrowed from 93 cm to 91 cm (mean difference of -2 cm, P <0.05), and 89 cm to 86 cm (mean difference of -3 cm, P =0.01) respectively. The National Cholesterol Education Program Third Adult Treatment Panel (NCEP ATP III) cut-off point for female WC is <88 cm. This means that the PAT group attained the NCEP ATP III guidelines for reducing central obesity-associated cardio and cerebrovascular risks during the short course of treatment.

Similarly, WHR declined by -0.03 (P <0.05, control group) and -0.03 (P =0.01, PAT group), from a ratio of 0.91 at visit 0 to the ratio of 0.88 at visit 1 (control group), and a ratio of 0.86 at visit 0 to the ratio of 0.83 at visit 1 (PAT group). The World Health Organisation (WHO) cut-off point for female WHR is ≤0.85 i.e. mean WHR for the PAT group at end-of-study achieved the recommended WHO range for women. In addition, the odds ratios (ORs) for at least one risk factor (type 2 diabetes, hypertension or atherogenic lipid disorders) are 5.4 (95% CI 2.44, 11.94) for WHR ≥0.90 and 4.38 (95% CI 2.24, 8.56) for WHR ranging between 0.85 - <0.90. This OR falls to 2.81 (95% CI 1.50, 5.26) in the WHR reference bracket of 0.80 - <0.85 [15]. Comparing to the OR in the top WHR bracket, ORs for WHR-associated metabolic diseases are 48% lower for the PAT group and 19% lower for the control group.

Clinical Markers	Control Group			PAT Group		
	Visit 0 (±SE)	Visit 1 (±SE)	Mean Difference (Paired *t* test)	Visit 0 (±SE)	Visit 1 (±SE)	Mean Difference (Paired *t* test)
Systolic BP (mmHg)	115 ±10	109 ±4	-6 (P >0.1)	116 ±7	112 ±2	-4 (P >0.05)
Diastolic BP (mmHg)	79 ±5	76 ±3	-3 (P >0.1)	79 ±4	75 ±1	-4 (P >0.1)
BMI (kg/m^2)	26.60 ±1.77	26.35 ±1.72	-0.25 (P <0.05)	26.60 ±1.62	26.25 ±1.81	-0.35 (P =0.01)
BF (%)	37.60 ±1.99	37.42 ±1.92	**-0.20** (P >0.05)	37.37 ±2.59	36.57 ±2.66	**-0.80** (P <0.001)
LMM (kg)	38.4 ±2.4	38.2 ±2.3	**-0.2** (P >0.05)	38.5 ±2.9	38.5 ±3.0	**0** (P >0.1)
WC (cm)	93.0 ±3.0	91.0 ±3.0	-2.0 (P <0.05)	89.0 ±7.0	86.0 ±6.5	-3.0 (P =0.01)
WHR	0.91 ±0.02	0.88 ±0.02	-0.03 (P <0.05)	0.86 ±0.02	0.83 ±0.01	-0.03 (P =0.01)

Table 1: Clinical markers at baseline (visit 0) and follow-up visit (visit 1) of control group (n =5) versus PAT group (n =10). Mean intervals between visits are 2.8 weeks and 2.9 weeks respectively. Key endpoint differences between control and PAT groups are shaded in black and grey.

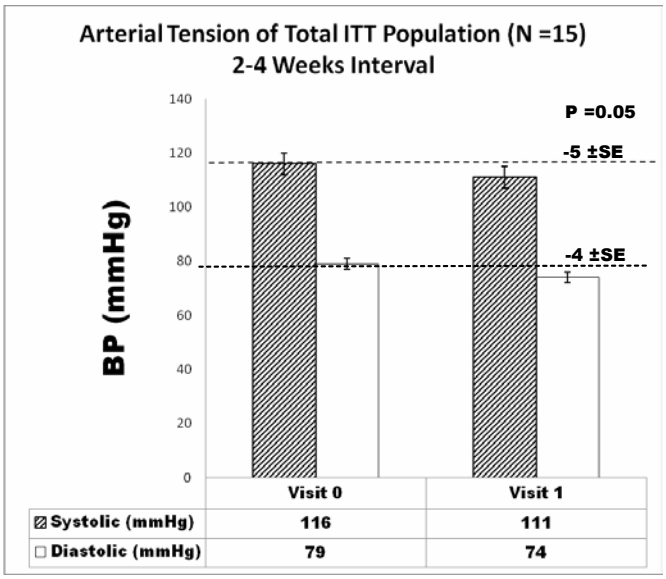

Figure 2: Systolic and diastolic BP-lowering effects in the total ITT population (N =15) over treatment intervals of 2-4 weeks.

Besides indicating the relative risks of developing type 2 diabetes, hypertension and lipid disorders, both WHR and WC are also independent risk factors for ischemic heart disease and stroke. As such, significant improvements in WC and WHR morphologic endpoints illustrate that energy tri-modulation at the molecular and physiological levels can translate into phenotypic changes that confer clinically relevant protection against the metabolic syndrome and its comorbidities.

However, reduction in body mass typically derives from both catabolism of protein and fat stores, leading to losses in both adipose (body fat) and muscle mass. Weight loss may even lead to an increase in overall adiposity and no improvement in apple shape (WHR), bringing about or further aggravating, sarcopenic obesity [16]. While both treatment arms in this study avoided the latter, the control group (n = 5) showed a marginal decline in LMM (-0.2 kg, P >0.05), even though this difference is not statistically significant.

In contrast, the PAT group (n = 10) achieved dual clinical benefits of 4-fold greater body fat loss (-0.8% in PAT group versus -0.2% in control group, P <0.001 and P >0.05 respectively) and protected muscle mass (0 kg loss in PAT group versus -0.2 kg in control group, with the null hypothesis valid in both treatment arms). Maintaining or improving lean muscle mass, while controlling adiposity and obesity, serves as a positive clinical marker for cardiometabolic health, insulin sensitivity and peripheral glucose disposal [17-20].

Arterial tension (BP) is also a surrogate (negative) clinical marker to assess renal, cardio- and cerebrovascular health risks. Hormone replacement therapy and treatment with anabolic steroids are associated with an increased risk of hypertension. Anorectic/anti-obesity agents may also aggravate BP. Conversely, the polyvalent medicine-augmented lifestyle intervention in the total ITT population was associated with a BP-lowering effect of -5/-4 mmHg (P =0.05) (Figure 2).

When analysed at group level, the arterial pressure readings were lowered, from 115/79 mmHg (visit 0) to 109/76 mmHg (visit 1) and 116/79 mmHg (visit 0) to 112/75 mmHg (visit 1) in both control and PAT groups respectively, although the hypotensive effects are not statistically significant (Table 1). A larger prospective study with sufficient power will be required to verify any BP-lowering effect. Notably, the use of phytoandrogens in the PAT group to modulate AR-mediated anabolic effects did not elevate arterial tension, nor antagonise BP-lowering effects of the polyvalent medicine-augmented lifestyle intervention, which were observed in the ITT population (Figure 2).

In conclusion, clinical solutions enabling patients to reach and sustain treatment targets for blood glucose, blood pressure and blood lipids are urgently needed, in light of the latest findings announced by the World Health Organisation (WHO) that the global percentage of patients reaching treatment goals are extremely low, despite being under treatment; and the established natural history of deteriorating physiological homeostasis within the metabolic cluster of type 2 diabetes, hypertension, obesity, adiposity, lipemia, atherosclerosis and cardio/cerebro/peripheral vascular disorders [21,22].

It is also clear that any long term strategy to protect the metabolic health of patients with type 2 diabetes, hypertension and other comorbidities, has to include lifestyle intervention. But, in reality, patients seek minimal change/effort, for any sustained compliance. The worsening MetS pandemic, in part, reflects the former. However, any 'minimalist effort' treatment must still address the requirement for patients to reach treatment goals for metabolic health.

Towards these ends, the results of this study present pioneering case-control evidence that use of PAT can potentiate aspects of metabolic health, via pleiotropic pharmacotherapy combined with minimalist lifestyle intervention. This shifts the emphasis away from drastic weight loss, restrictive dieting and strenuous exercise that would otherwise require greater degrees of effort from patients.

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