

Investigating the Association of Metabolic Syndrome with Pre-eclampsia

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Abstract

Introduction: Metabolic syndrome shown to be associated with increased inflammatory state and pre-eclampsia in pregnant women in the western population. Association between metabolic syndrome and its components with pre-eclampsia is yet to be determined in Indian population.

Objective: The aim was to investigate the association between metabolic syndrome and its components with pre-eclampsia.

Methods: A case-control study was designed with cases who had gestational hypertension or pre-eclampsia and controls were normal term deliveries. Clinical data and maternal serum were collected. The presence of metabolic syndrome (3/5 variables present) and a metabolic score (continuous 0-5) were investigated. Significant associations were evaluated using *t*-tests, and Pearson Chi-square tests of association.

Results: A total of 100 cases and 265 controls were evaluated. We observed a higher odds of pre-eclampsia when metabolic syndrome was present (adjusted odds ratio [AOR] = 2.71 [1.1-6.67], *P* = 0.03). For every one-unit increase in metabolic score, there was a 39% increased odds of pre-eclampsia (AOR = 1.39 [1.06-1.82], *P* = 0.017).

Conclusions: Metabolic syndrome was found to be associated with pre-eclampsia. For the presence of every parameter of metabolic syndrome present, increased the risk of pre-eclampsia.

Keywords: Cardiovascular disease risk, Metabolic syndrome, Pre-eclampsia

INTRODUCTION

Pre-eclampsia continues to be a major cause of maternal and perinatal morbidity and mortality. In India, hypertensive disease continues to be the majority of maternal death in live births.¹ Despite continued research, the etiology of this pregnancy specific disease remains unknown. Broadly, pre-eclampsia is a disease resulting in hypertension and proteinuria. However, pre-eclampsia encompasses a wide range of clinical phenotypes with varying degrees of severity. More severe disease causing multi-system injury and/or eclampsia is largely the cause of maternal mortality.

Despite significant efforts to elucidate the pathophysiology of this complex disease, we currently have neither a valid diagnostic test nor a proven intervention likely due to our poor understanding of the mechanisms involved in the development of pre-eclampsia. On the basis of a shared phenotype of hypertension, common risk factors²⁻⁵ and

the observed link between pre-eclampsia and future cardiovascular risk,^{1,6,7} biological pathways implicated in cardiovascular disease (CVD) are an important source for understanding potential etiologic pathways involved in the development of pre-eclampsia. The metabolic syndrome is a clustering of metabolic and CVD risk factor abnormalities with a shared patho-physiology that has demonstrated utility in the non-pregnant population. The metabolic syndrome—an aggregate of risks—confers an increased risk of developing Type 2 diabetes and complex CVD, which appears to be beyond that related to the individual metabolic components.⁸⁻¹¹ The National Cholesterol Education Program (NCEP)-adult treatment panel (ATP III) guidelines, which have gained widespread clinical use, define metabolic syndrome as three or more of five clinically ascertained risk factors: Abdominal obesity, low high density lipoprotein-C (HDL), elevated triglycerides (TG), blood pressure and fasting glucose.¹¹ To enunciate underlying pathophysiology and the synergistic

effects of the components, this relationship has been conceptualized as “metabolic syndrome.” The metabolic syndrome concept (aggregate of risk factors) has already demonstrated clinical utility in the non-pregnant population to assess CVD risk.

We have performed the following studies to further evaluate the association between metabolic syndrome (using both clinical and laboratory criteria) and pre-eclampsia. We hypothesize that the metabolic syndrome was associated with pre-eclampsia. Determining an association, between known cardiovascular risk factors in non-pregnant women (metabolic syndrome) and pre-eclampsia may significantly advance our ability to understand the pathophysiology and potentially predict the development of pre-eclampsia.

METHODS

This case-control study, was performed at the hospital of Basaveshwara medical college and research center, Chitradurga, in Karnataka, between September 2013 and August 2014. Cases were women with gestational hypertension or pre-eclampsia. Controls were women presenting for delivery at term. All women admitted to labor and delivery with gestational hypertension or pre-eclampsia were enrolled after obtaining the consent. Cases (gestational hypertension or pre-eclampsia) were identified based on pre-specified maternal according to ACOG criteria.⁸ Pre-eclampsia included the diagnosis of gestational hypertension and was defined as elevated blood pressure ($\geq 140/90$ mmHg on two measurements ≥ 6 h apart) with $\geq 1+$ proteinuria (0 - trace protein for gestational hypertension). Preterm pre-eclampsia was defined as a delivery before 34 weeks because of pre-eclampsia. Controls were enrolled from women presenting for delivery at term (≥ 37 weeks) for spontaneous.

Rupture of membranes, term labor, induction of labor or caesarean section. Multiple gestation pregnancies were not included in this analysis. Information regarding height, weight and history of chronic hypertension (CHTN), diabetes mellitus collected and any other medical condition was collected. Serum was collected at or within 24 h of enrolment for both cases and controls. HDL and TG were measured enzymatically on a Hitachi 912 auto analyzer (Roche diagnostics).

Metabolic syndrome is composed of the five NCEP-ATP III laboratory and clinical criteria that have previously been extensively reported: (1) Blood pressure, (2) fasting glucose (as a measure of insulin resistance and/or glucose intolerance), (3) obesity (measured as hip to waist ratio or body mass index (BMI ≥ 30)), (4) HDL and (5) TG.⁹

Considering these variables were being assessed during pregnancy, some modifications were necessarily made. For the blood pressure variable, the diagnosis of elevated blood pressure or CHTN was made by prior history or if a patient screened at ≤ 20 weeks gestation with ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic blood pressure. The presence of pre-gestational or gestational diabetes was used as a measure/surrogated for insulin resistance/fasting glucose. Any woman with a history of pre-gestational diabetes or any woman who tested positive for gestational diabetes was considered positive for this factor. For the variable of obesity, we utilized BMI (calculated using reported height and weight at the last prenatal visit- kg/m^2) given the impracticality of waist circumference measurement or hip-waist ratio in gravid women. BMI ≥ 30 is utilized in the World Health Organization diagnosis of metabolic syndrome thus validating this approach.^{10,11} Clinical endpoints for HDL and TG were based on non-pregnant definitions but then TG levels were modified by reports of lipid levels in pregnancy.¹²

Thus, our definition of metabolic syndrome included the following components: (1) pre-existing hypertension, (2) diabetes (gestational or pre-gestational), (3) BMI ≥ 30 at last prenatal visit before delivery, (4) HDL ≤ 50 and (5) TG ≥ 250 . On the basis of non-pregnant literature, the presence of metabolic syndrome was defined as having three of the five variables assessed “present” using the clinical cut-offs defined above. To explore the components of the metabolic syndrome beyond the dichotomization that is routinely performed in the non-pregnant population, a metabolic score (continuous variable 0-5) was explored to assess its association with pre-eclampsia. The prevalence of the metabolic score among cases and controls and initial descriptive analyses were performed using *t*-tests, or Wilcoxon rank sum tests for nonparametric data and Pearson chi-square tests of association.

RESULTS

One hundred pre-eclamptic cases and 265 controls were evaluated. The demographics and clinical profile are shown in Table 1. The prevalence and unadjusted odds ratios for individual components of the metabolic score are shown in Table 2. HDL ≥ 50 was significantly associated with pre-eclampsia. Nearly, 30% of the cases had an HDL of >50 . The prevalence of obesity in our population was similar between the cases and controls. There was no significant interaction between metabolic score and maternal age. When each component of the metabolic score was further evaluated, an interaction was demonstrated between obesity and age, but not with any other components of the full five component metabolic

score. Figure 1 demonstrates the prevalence of metabolic score 0-5 in cases and controls. Only 4.9% of controls when compared with 10.9% of cases had metabolic syndrome (3/5 variables present, $P = 0.037$). The association between metabolic syndrome and pre-eclampsia remained significant (adjusted odds ratio [AOR] = 2.71 [1.1-6.67], $P = 0.03$) after controlling for race, age, parity and gestational age at screen. To explore the metabolic score in pregnancy further, we evaluated it as a continuous variable. For every one-unit increase in metabolic score, there was a 39% increased odds of having pre-eclampsia (AOR = 1.39 [1.06-1.82], $P = 0.017$) after controlling for the same confounders. These associations persisted and were even stronger when analyses were restricted to only full term patients (Metabolic syndrome AOR = 3.41 [1.19-9.75], $P = 0.02$; Metabolic score (AOR = 1.68 [1.08-2.61], $P = 0.02$). Given the significant association of both the metabolic syndrome and score, the laboratory components of these aggregate measures were further investigated. Figure 2 demonstrates the distribution of HDL and TG in cases and controls. Median HDL significantly differed between cases and controls 59.9 mg/dl versus 65 mg/dl; $P = 0.005$). There was no difference in median TG level between cases and controls (176 mg/dl versus 176 mg/dl; $P = 0.76$). Women with pre-eclampsia had a two-fold higher odds of having an HDL ≤ 50 compared with controls (AOR=2.27,[1.28-4.00], $P=0.005$) after adjusting for parity, maternal age, and BMI at final prenatal visit. When HDL was evaluated further, no cases had an HDL >100 , whereas 3% of controls ($P =$

0.08) had HDL levels above 100. When restricting the analysis to only women with a history of pre-eclampsia, the median HDL was 54 in cases and 62 in controls ($P = 0.74$). When only women without CHTN were included in the analysis, cases still had a lower median HDL when compared to controls (58.5 vs. 64; $P = 0.01$). More specifically, in women without CHTN, those with an HDL < 50 had a two-fold higher odds of having pre-eclampsia (AOR = 1.99 [1.10-3.61], $P = 0.023$) after controlling for age, parity, BMI and gestational age at prenatal screen. When restricted to full term patients only, cases also had a lower median HDL when compared with controls (58 mg/dl vs. 68 mg/dl; $P = 0.005$). Specifically, in term patients, women with an HDL ≤ 50 had a 2.7 fold higher odds of having pre-eclampsia (AOR = 2.70 [1.38-5.29], $P = 0.004$) when adjusting for the same confounders. To further understand the association between pre-eclampsia and HDL, a subanalysis only within control patients was performed.

Table 1: Demographic and clinical profile

	Cases	Controls	P value
Mean age (years)	27.3	27.2	0.89
Age >25 years	36.6 (37)	32.6 (87)	0.46
Primiparous	56.4 (57)	32.6 (87)	<0.001
Mean gestational age at delivery (weeks)	36.6	39.1	<0.001
History: Pre-eclampsia	38.6 (17)*	12.8 (23)†	<0.001
History: Preterm delivery	25.0 (11)*	13.9 (25)†	0.07

*Calculated using denominator 43. †Calculated using denominator 179

Table 2: Metabolic syndrome components

	Cases % (N=101)	Controls % (N=267)	Un AOR	P value
CHTN	6.9 (7)	5.2 (14)	1.35	0.53
All diabetes	5.9 (6)	4.1 (11)	1.47	0.46
Pregest DM 2	2 (2)	2.6 (7)	0.75	0.72
Gest DM	4 (4)	1.5 (4)	2.69	0.15
HDL ≥ 50	28.7 (29)	15.7 (42)	2.16	0.005
TG ≥ 250	21.8 (22)	16.1 (43)	1.45	0.20
Final BMI ≥ 30	59.4 (60)	58.8 (157)	1.02	0.92
Metabolic syndrome (≥ 3 factors present)	10.9 (11)	4.9 (13)	2.39	0.04

TG: Triglycerides, BMI: Body mass index, CHTN: Chronic hypertension, DM: Diabetes mellitus, HDL: High density lipoprotein, AOR: Adjusted odds ratio

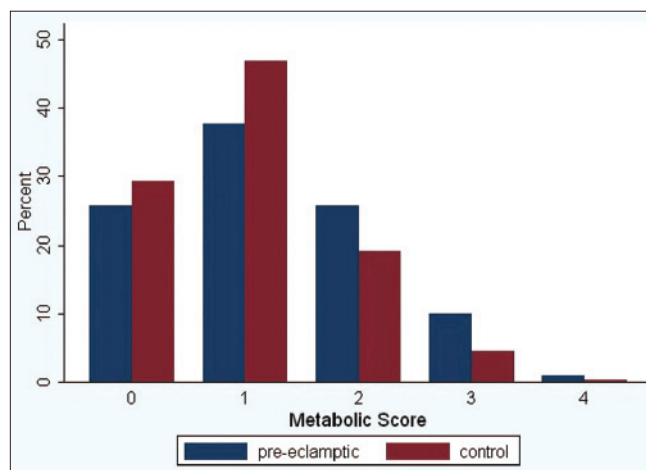


Figure 1: Distribution of metabolic syndrome and score in cases and controls

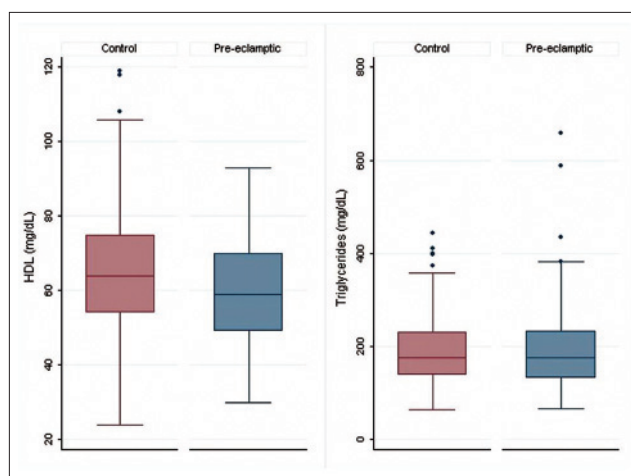


Figure 2: Distribution of high-density lipoprotein and triglycerides in cases and controls

In control patients, 26% of those with a history of PEC had an HDL ≤ 50 when compared with 14.8% those without a history of pre-eclampsia ($P = 0.15$).

Additional within case analyses were explored comparing women with preterm disease ($n = 13$) to those without ($n = 88$) and those with recurrent pre-eclampsia ($n = 17$) to those without ($n = 84$). There was no significant difference in the metabolic score when comparing preterm cases to cases delivered ≥ 34 weeks. Within cases, the distribution of metabolic score was different when comparing women with a history of pre-eclampsia to those without a history (P value for trend = 0.027). Specifically, 5.8%, 41.2%, 29.4%, 17.6%, and 5.8% of women with a history of pre-eclampsia had a score of 0-4, respectively, when compared with 29.6%, 40.7%, 22.2%, 7.4% and 0% in women without a history of pre-eclampsia. Within cases again, 7% of women without a pre-eclampsia history had metabolic syndrome versus 23.5% of women with a history of pre-eclampsia ($P = 0.13$).

DISCUSSION

Literature is scant regarding association of metabolic syndrome or the components of the syndrome with pre-eclampsia.^{13,14} The association between some of the individual components of the score and pre-eclampsia has been demonstrated.^{2,4} However, all the components of metabolic syndrome have not been assessed at the same time in a prospectively identified population nor has the concept of a synergistic risk of these components into a “score” been evaluated in pregnancy. This Indian study demonstrates that the concept of metabolic syndrome (aggregate risk concept), including all the variables reported in the non-pregnant literature, and the alternative continuous measure (metabolic score) are independently associated with pre-eclampsia. Further, lower HDL levels and increased metabolic score in the cases may indicate pathogenesis of disease. Although we cannot say whether the lower HDL levels observed are because of pre-eclampsia, the overall results and those within the controls stratifying by a history of pre-eclampsia suggest that dyslipidemia may be involved in the pathogenesis of pre-eclampsia. The utility of the metabolic syndrome concept for risk stratification in the young non-pregnant population¹⁵ and the observed similarities between CVD and pre-eclampsia suggest its potential usefulness in the pregnant population. This association between pre-eclampsia and metabolic syndrome is stronger than the association with CHTN or lipids alone suggesting an added benefit to the aggregate syndrome concept over individual risk factors alone. Using a metabolic score versus the traditional definition of metabolic syndrome in pregnancy, may allow for better prediction of both pre-

eclampsia development and in identifying those at risk for future CVD.

Strengths of our study include the prospective identification of cases, a large number of patients and a uniquely Indian population. We made diagnoses using a priori definitions. The size of our study allowed for restricted analyses and secondary analyses comparing high-risk subgroups of women within the cases. There are limitations to our study that must be mentioned. Despite the relatively large numbers enrolled, we are unable to evaluate definitively which components of the metabolic score contribute to the additional observed risk because of the low prevalence of each factor. As such, the components could only be considered as equally weighted contributors to the summary score in this study. Further, the laboratory tests used as part of the metabolic score were not obtained as fasting samples. However, non-fasting levels have been demonstrated to correlate with fasting levels and have been demonstrated to have clinical utility in obstetrical studies.¹² Also, both TG and HDL cholesterol are known to increase during pregnancy making risk assessment gestational age dependent.^{13,16} However, the decreased HDL findings were consistently observed when analyses were restricted to only term patients, strengthening our findings. There is controversy in whether to include “gestational hypertensive patients” (those patients without proteinuria) in studying pre-eclampsia. However, the clinical line is ambiguous given 20% of eclamptic patients do not have protein and it is not known whether gestational hypertension is truly a separate entity. Further, the inclusion of these patients makes our results more generalizable and if women with gestational hypertension are truly at lower risk, their inclusion should have biased our findings to the null. This same possibility of misclassification is applicable to women with CHTN. The diagnosis of pre-eclampsia in a woman with pre-existing CHTN is difficult and thus is subject to misclassification. However, the consistency of our results in analyses restricted to women without chronic hypertension, strengthens our findings. Finally, we did not match controls by gestational age because women with preterm birth appear to have increased long-term cardiovascular risk when compared with women with term deliveries, making them a less than ideal control group.² To address this, the consistency of our results when restricted to women with pre-eclampsia at term confirms and strengthens our findings.

Recent studies have demonstrated that pre-eclampsia appears to confer a lifetime increased risk of maternal mortality and morbidity from CVD. Whether pre-eclampsia represents a “failed stress test” for later complex CVD or whether pre-eclampsia itself alters a patient’s physiology predisposing her to CVD,¹⁷ is yet to be seen. Like CVD, pre-eclampsia may be the endpoint of many diverse

patho-physiologic processes that are highly interdependent. It has been theorized that metabolic syndrome could be a causal link that explains the increased lifetime risk of CVD in some women with pre-eclampsia.¹⁸⁻²⁰ Perhaps, pre-eclampsia is an early manifestation of CVD and abnormalities in pathways involved in metabolic syndrome are causative to both pre-eclampsia and CVD in some women. Our findings with respect to a significant association with metabolic score, women with recurrent pre-eclampsia, and women with a history of pre-eclampsia in the control group further strengthens this hypothesis. Conversely, metabolic syndrome or score is not present in all women who have pre-eclampsia further demonstrating the complex nature of the disease. In these women, other risk factors and pathways to disease development may play a more prominent role in the etiology.

The concept of the metabolic score may not only aid in the identification of women at risk for developing pre-eclampsia but may also help with CVD risk stratification and may provide a new window of opportunity to decrease CVD. In women aged 25-44, there is a paucity of research identifying risk factors for cardiovascular morbidity and mortality-thus intervention strategies cannot begin. Specifically addressing cardiovascular risk factors in young women before the clinical onset of disease is a novel approach to also understanding future CVD risk in women. Continued research targeted at better understanding the causal pathways common to pre-eclampsia and CVD is warranted. Specifically, future studies should assess the ability of the metabolic score in predicting the development of pre-eclampsia, as well as future CVD, particularly in patients with preterm and recurrent disease. Subsequent trials should assess interventions that modify the metabolic score in high-risk women to determine whether pre-eclampsia and future CVD risk is reduced. Interventions such as weight loss prior to pregnancy, the use of oral hypoglycemics or other agents and/or more targeted anti-hypertensive medications may be promising to prevent both preeclampsia and future CVD.

CONCLUSION

Metabolic syndrome was found to be associated with pre-eclampsia. For the presence of every parameter of metabolic syndrome present, there is increased the risk of pre-eclampsia. Further-more research in this can be performed.

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How to cite this article: Poornima M, Rakesh B. Investigating the Association of Metabolic Syndrome with Pre-eclampsia. *Int J Sci Stud* 2014;2(7):1-5.

Source of Support: Nil, **Conflict of Interest:** None declared.