

## Association of Serum Homocysteine, Vitamin B12 and Folic Acid Levels with Metabolic Syndrome

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Sir,

I read the article "Serum Homocysteine, Vitamin B12 and Folic acid levels in patients with Metabolic syndrome" with great interest.<sup>1</sup> Metabolic syndrome has drawn attention of researchers because of its association with athero vascular diseases. It has been found that there is a high prevalence of metabolic syndrome in Indians. A multisite study from India reported age adjusted prevalence of metabolic syndrome in men and women as high as 33.3% and 40.4% respectively.<sup>2</sup> Even vitamin B12 deficiency and hyperhomocysteinemia are common problems encountered in Indian population. One of the study from Pune, Maharashtra found that 81% of urban middle class individuals had low vitamin B12 concentrations and 79% had hyperhomocysteinemia.<sup>3</sup> Interestingly, it has also been hypothesized that low levels of vitamin B12 and folic acid along with hyperhomocysteinemia are associated with athero vascular diseases. Supported by these facts, Narang et al conducted this study to determine the levels of these aforementioned parameters in individuals with and without metabolic syndrome. They concluded that Indian patients with metabolic syndrome have a strong association with elevated blood levels of homocysteine and reduced levels of vitamin B12 and folic acid. However, it is pertinent to note the limitations of this study enumerated below -

1. The authors have utilized the American Heart Association guidelines to define metabolic syndrome. It has been demonstrated that Asian Indians are likely to develop insulin resistance and cardiovascular risk factors at lower levels of Body Mass Index (BMI). The cut off levels of BMI for overweight and obesity have been revised for Asian Indians to 23.0 - 24.9 Kg/m<sup>2</sup> and > 25 Kg/m<sup>2</sup> respectively. The recommended

action level 1 waist circumference cutoffs for Asian Indians are 78 cm for men and 72 cm for women [4]. Interestingly, the mean ( $\pm$  standard deviation) BMI for the controls was 23.04 ( $\pm$  0.829) Kg/m<sup>2</sup> and the waist circumference ( $\pm$  standard deviation) for controls was 78.8 ( $\pm$  5.664) cm. If guidelines for Asian Indians were utilized in this study then all these controls will also fall in overweight category. Thus, it would have been more practical if guidelines pertaining to our country were put to use to identify this category of patients. This would have helped to identify the risk factors with an Indian perspective.

2. The inclusion criteria spells out that patients with metabolic syndrome were recruited as cases for the study. The mean ( $\pm$  standard deviation) fasting blood sugar for the cases was 137.72 ( $\pm$  26.835) mg/dl. There is a high likelihood that the cases were started on metformin given that their mean ( $\pm$  standard deviation) body mass index was 29.316 ( $\pm$  1.645) kg/m<sup>2</sup>. It is known that long term metformin use increases the risk of vitamin B12 deficiency which in turn results in raised homocysteine concentrations.<sup>5</sup> As the authors have not excluded cases taking metformin in their protocol, a significant bias may have been introduced into the study interpretation.
3. The authors have presented their non-normally distributed quantitative data as mean  $\pm$  standard deviation. However, it is not recommended to assume that mean will be the middle of the sample or that most of the sample will lie within two standard deviation on either side of mean in a non-normally distributed data.<sup>6</sup> It is recommended to utilize median with interquartile range to present quantitative variables in such a scenario to make it more meaningful for the readers. In fact Mann Whitney U nonparametric test, the one employed by the authors to test the significance, compares the medians of the two groups rather than the means.

The present study provides important data for the researchers to

interpret and analyze the relationship between metabolic syndrome, vitamin B12, folic acid and homocysteine levels. Presentation of quantitative data as medians with interquartile range would have been more meaningful. However, it would have been more interesting to analyze metabolic syndrome as per the guidelines for Asian Indians. Besides, consideration for use of metformin as an exclusion criteria may change the results all together. Future studies may be planned accordingly.

### References

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### Reply from Author

**M Narang**

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Sir,

Dr Gulati has reiterated the need for studies on vitamin B12, folic acid and homocysteine in patients with metabolic syndrome. Regarding the points mentioned as limitations of this study, we have following observations:

1. On the issue of definition of metabolic syndrome for Indians and other South Asians, we feel that the objection is unwarranted since the definition used by us, i.e. American Heart Association (AHA) definition with cut-offs for Asians as mentioned in footnote of its Table 2, defines abdominal obesity in the same manner as proposed by Misra et al in their consensus statement, i.e. waist circumference cut-offs of 90 cm for men and 80 cm for women (Table 2 of Misra et al).<sup>1-3</sup> These cut-offs are also recommended in the International Diabetes Federation (IDF) definition.<sup>4</sup> In 2009, a joint statement by IDF,

AHA, National Heart Lung and Blood Institute and 3 more societies has been published to provide a harmonious definition of metabolic syndrome.<sup>5</sup> This statement also recommends the same waist circumference criteria for Asians. Most recent studies from India have also used these cut-offs.<sup>6,7</sup> Waist circumference cut-offs of 78 cm for men and 72 cm for women have been given by Misra et al for Action level 1 (avoid gaining weight and maintain physical activity) but not for defining metabolic syndrome. According to authors themselves, even these Action level 1 criteria need to be researched further. Body mass index is not used for diagnosing metabolic syndrome in any of these definitions.

2. Whether or not patients were taking metformin cannot be concluded on basis of fasting blood sugar and body mass index. Although, metformin has been reported to increase the risk of vitamin B12 deficiency, this is seen in only about 4% of patients taking metformin.<sup>8</sup> Hence, it is unlikely that our findings would have been markedly different had we excluded patients on metformin. Even if vitamin B12 levels are reduced due to metformin, it is important to document, characterize and research this aspect, rather than excluding such patients from studies. Moreover,

folic acid, which is also involved in homocysteine metabolism, was also low in patients with metabolic syndrome in our study.

3. Amongst the large data we reported in this study (27 variables are listed in table 1 of our study), some were normally distributed and others were not. Hence, we gave mean and standard deviation for all for the sake of simplicity rather than mentioning medians with inter-quartile ranges for some of the data and mean with standard deviation for the rest. Non-parametric statistical tests, e.g. Mann-Whitney U test, were used for analysis of non-normally distributed data.

## References

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