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### Author reply

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### Asymmetric dimethylarginine levels decrease because of insulin infusion: is it an unexpected finding?

In their recent article, Eid et al [1] hypothesized that acute infusion of insulin would increase asymmetric dimethylarginine (ADMA) levels in a group of young men with mildly elevated blood pressures. Their assumption was based on the previous findings showing that patients with insulin resistance (IR) had high ADMA levels [2,3]. In our previous report on patients with chronic kidney disease, we also measured high ADMA and insulin levels that were positively correlated [4]. However, the association between insulin and ADMA levels in these reports does not necessarily mean that insulin itself is the cause of ADMA elevation. It is not the insulin but the lack of insulin effect, namely, the presence of IR, which probably has a role in the elevation of ADMA.

Dandona et al [5] have shown that insulin has significant anti-inflammatory and vasodilatory properties. Insulin increases the expression of endothelial nitric oxide synthase [6] and the release of nitric oxide [7,8] from the vascular endothelium in a dose-dependent manner. At this point, the findings of Eid et al [1] complement the previous *in vitro* reports and help us to understand the mechanism of the beneficial effects of insulin on the vascular endothelium. However, we should keep in mind that this study was performed in young men with mildly elevated blood pressures, who are most likely to be insulin sensitive. It is well reported that IR is present only in half of the hypertensive population [9]. In our previous studies, we did not observe IR in young patients with new-onset, uncomplicated hypertension [10–12]. Therefore, it would be interesting to design a further study to investigate the effect of insulin infusion on distinct group of patients with and without IR.

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### Author reply: phenotype of subjects with type 2 diabetes mellitus may determine clinical response to chromium supplementation

With interest, we read the article by Wang et al [1] about trying to find a tool for selecting patients who are responsive to chromium supplementation and those who are not. We fully agree that it is important to be able to have some kind of parameter by which you can select patients who have a low chromium status, as there are no possibilities yet to define someone as chromium deficient [2]. This would indeed be more appropriate than performing more and more randomized controlled trials in unselected patients in whom it seems that, in most high-quality trials, there were no beneficial effects [3].

However, there are some important points that need clarification to be able to interpret the results accurately. Firstly, the dependent variable used in this article is the difference between insulin sensitivity measured at the end and beginning of the 6-month study. The only subject variable significantly associated with this difference is the baseline insulin sensitivity. It is not surprising that this baseline variable is associated with a change of the same variable. We would like the authors to clarify this. It would be perhaps more informative to know if patients who were relatively more insulin resistant at baseline had a more

beneficial effect on hemoglobin A<sub>1c</sub> and if this was more pronounced in the chromium group than in the placebo group.

Secondly, we would like to ask the authors to look beyond their results. How would they advise researchers (and clinical physicians) performing future human chromium research to select patients? If it will be concluded from future research that chromium has beneficial effects in specific subgroups of subjects with type 2 diabetes mellitus, we would like to select such patients in daily routine outpatient care, which would not likely include insulin clamp procedures. Would their results be the same when using a homeostasis model assessment equation?

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