Author's response to reviews

Title: The relation between insulin resistance and lung function: a cross sectional study

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Author's response to reviews: see over
Dear Editor

Here are point-by-point response to the concerns of reviewers and editor. Thank you for giving me opportunity to revise the manuscript for preparing a better article.

Hypothesis of the study was specified at the last paragraph of Background section. Abstract and Background were tailored according to suggestions of reviewer. Unnecessary details like measurement of lung volumes by plethysmography was deleted from Method section. Study cohort was summarized, and grammatical errors were corrected. All results were removed from Discussion section and replaced to Results section. P values were removed from discussion. The sentences were corrected at the discussion section according to reported results of the manuscript as suggested. Total column was replaced as first column and cut off values were placed at the Table1. Sampling method and inclusion of patients were specified. The measuring methods of laboratory parameters and reference regarding calculation of insulin resistance were placed at the Method section. Definition of obstructive and restrictive diseases was corrected. Column aligment of Table2. was corrected. References were formatted. Rationale for hypothesis was revised. Acknowledgement section was revised as stated. Ethical committee protocol number of manuscript was placed in the manuscript.

A professional language editing service with native english speaker was used for edition of the manuscript.

14.07.2015

Kind regards,

Assoc. Prof. Gul Sagun; MD
Reviewer's report
Title: The relation between insulin resistance and respiratory function
Version: 2
Date: 27 April 2015
Reviewer: Deepa Rastogi

Reviewer's report:
My review is summarized below.

Comments to the authors:
Sagun et. al report on the association of insulin resistance with metabolic abnormalities and with pulmonary function in a cohort of Turkish adults followed at a single center. My biggest concern is the assumption on the authors that pulmonary function is predictive of insulin resistance. Since their’s is a cross-sectional study, the reverse may well be true as well. Insulin resistance may be predictive of pulmonary function abnormalities. In fact several statements by the authors in the introduction suggest that metabolic syndrome/glucose abnormalities are associated with pulmonary function abnormalities. Why have the authors developed the hypothesis that they did?

Hypothesis of the study was specified at the last paragraph of Background section.

Although as seen above, studies about the relation of lung function, diabetes, and MetS are plentiful, but studies about the relationship of insulin resistance and lung function are scarce. There have not been any studies evaluating lung functions in patients with insulin resistance in Turkey. The aim of the present cross-sectional study was to evaluate lung functions according to insulin resistance states in outpatients without respiratory disease admitted to internal medicine clinics in Turkey.

Abstract: the authors report on the association of insulin resistance with cardiovascular morbidity but the manuscript does not have anything to do with CVS morbidity or the association between insulin resistance, pulmonary function and CVS morbidity. Please tailor the introduction to the point of focus for the manuscript.

The same point detailed above is applicable for the introduction. The introduction needs to be focused on the specific point of the manuscript.

Abstract and Background were tailored according to suggestions of reviewer.

Abstract

Background: Impaired lung function and insulin resistance have been associated and thereby have also been indicated to be powerful predictors of cardiovascular mortality. Therefore, the co-existence of insulin resistance and impaired lung function accompanied with cardiovascular risk factors should induce cardiovascular mortality even in patients without known respiratory disease in a cumulative pattern. It could be useful to determine the lung function of patients with insulin resistance in order to decrease cardiovascular mortality by means of taking measures that minimize the risk of decline in lung function.

Conclusions: Insulin resistance should also be considered amongst the contributing factors for decline in lung function.

Impaired lung function, as measured by forced vital capacity (FVC) or forced expiratory volume in the first second (FEV1) [1] has been indicated as not only a marker of premature
death from all causes [2] but also has been associated with excess adiposity, insulin resistance, MetS, and type 2 diabetes mellitus. All these conditions have also been indicated to be powerful predictors of nonfatal ischemic heart disease and cardiovascular mortality [1, 3-6].

Insulin resistance, beta cell dysfunction, impaired glucose tolerance, and MetS ultimately lead to T2DM. In other words, insulin resistance has been associated with a range of cardiovascular risk factors including dyslipidemia, essential hypertension, glucose intolerance, and diabetes [7].

Methods: the authors report on measurement of lung volumes by plethysmography but do not report that in the manuscript. If not included, please delete unnecessary details from methods.

Unnecessary details like measurement of lung volumes by plethysmography was deleted from Method section.

Results: Description of the study cohort should be summarized in Table 1 and differences should be described without inclusion of specific numbers in the description. As currently written, the sentences are broken up and not lucid. In keeping with my concerns about the hypothesis, the authors have chosen to include the participants based on their insulin status and therefore, it seems that that should be the predictor variable rather than the outcome variable.

Unnecessary details like measurement of lung volumes by plethysmography was deleted from Method section.

Results: Description of the study cohort should be summarized in Table 1 and differences should be described without inclusion of specific numbers in the description. As currently written, the sentences are broken up and not lucid. In keeping with my concerns about the hypothesis, the authors have chosen to include the participants based on their insulin status and therefore, it seems that that should be the predictor variable rather than the outcome variable.

Study cohort was summarized. Sentences were corrected

Results

Demographics and anthropometrics in study groups

Patients with and without insulin resistance were homogenous in terms of gender and age. Insulin resistance was present in 36.8% of patients. Mean±SD values for BMI (body mass index) (37.0±5.8 vs. 33.4±5.2 kg/m², p<0.001), percentage of patients with BMI of ≥35 kg/m² (61.9 vs. 28.7%, p<0.001), and Mean±SD values for waist circumference (107.0±11.5 vs. 98.3±9.8 cm, p<0.001) were significantly higher in patients with than without insulin resistance (Table 1).

Discussion. Please remove all results from the discussion and include them under the results section (paragraph 2 of discussion). If already in the results, remove the p values from the discussion. In keeping with my concern about the way the hypothesis is stated, the authors suggest that insulin resistance is a predictor of pulmonary function deficits in line 258 on page 11, which is the opposite of the direction of association that they have reported in their manuscript. The same is repeated in lines 317-318, page 13.

All results were removed from Discussion section and replaced to Results section. P values were removed from discussion. The sentences were corrected at the discussion section according to reported results of the manuscript as suggested.
Hence, in our study population, that insulin resistance was negatively correlated with lung function seems notable and supports the suggestion that the metabolic pathways related to insulin resistance are crucial in initiating lung abnormalities in type 2 diabetic patients [15].

While the exact mechanisms by which a state of insulin resistance leads to low lung function as well as the value of introducing lung function measures into an insulin resistance prediction model remain to be elucidated, our findings emphasize that FEV1/FVC% is low, thereby indicating an obstructive respiratory pattern in the interaction between lung dysfunction and insulin resistance.

Table 1. Total should be the first column followed by the two groups of interest. Instead of raised blood pressure, blood glucose etc, please place the cut off value and state those above the cut off value (>…x mmHg for BP, x mg/dl of glucose etc..)

‘Total’ column was replaced as first column and cut off values were placed at the Table1. The parameters of metabolic syndrome were revised.

Minor comments:
The authors should seek help from a person familiar with scientific writing. The introduction is broken into single sentence paragraphs and there are several grammatical corrections that need to be made throughout the manuscript.

A professional language editing service with native english speaker was used for edition of the manuscript.

**Level of interest:** An article of limited interest
**Quality of written English:** Needs some language corrections before being published

**Reviewer's report**
**Title:** The relation between insulin resistance and respiratory function
**Version:** 2  **Date:** 27 March 2015
**Reviewer:** Joyashree Banerjee
**Reviewer's report:**
Major Compulsory Revisions
1. There are some methodological weaknesses, which invalidate the expressed result and conclusions. In Materials and methods study population is not well defined, Inclusion criteria should be specified that included patients.
2. The authors do not specify the sampling method.

Sampling method and inclusion of patients were specified. (like consecutively, patients were non-smokers)

3. How fasting serum insulin and fasting plasma glucose and lipid profile were measured?
The measuring methods of laboratory parameters and reference regarding calculation of insulin resistance were placed at the Method section.

Blood specimens were collected after 12-16 hours of fasting. Roche Cobas 8000 analyzer was used for fasting plasma glucose (intra-assay cv % 1.7 and 0.7 for low and high concentrations respectively), triglycerides (intra-assay cv % 0.9 and 0.6 for low and high concentrations respectively), and HDL-C (intra-assay cv % 0.8 and 0.6 for low and high concentrations respectively). Beckman Coulter Unicel Dxl 800 (intra-assay cv % 5.6, 4.5, and 3.1 for normal, intermediate, and high concentrations respectively) was used for insulin assay. Primus MRDV with HPLC technique was used for HbA1c (intra-assay cv % 0.82, 0.91, and 0.46 for normal, intermediate, and high concentrations respectively; inter-assay cv % 2.91, 1.79, and 1.09 for normal, intermediate, and high concentrations respectively).

The authors have not given any reference regarding insulin resistance. For definition of insulin resistance a reference is required.

Corrected as following.

Insulin resistance was calculated using the homeostasis model assessment insulin resistance index (HOMA-IR) according to the following formula: fasting plasma glucose (mmol/L) x fasting serum insulin (mU/ml)/22.5 [18]. (18- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985, 28:412-419.

4. Authors mentioned in 161 and 162 line that the ratio of FEV1 to FVC (FEV1/FVC) was calculated, and a value #0.70 was considered as normal. In my opinion this is not the normal value of FEV1/FVC, Restrictive as well as obstructive diseases are not well defined.

Definition of obstructive and restrictive diseases was corrected.

The ratio of FEV1 to FVC (FEV1/FVC) was calculated, and a value ≥70% was considered as normal. According to a modified classification of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), patients were classified as having normal spirometric values (FEV1/FVC ≥ 70 %, FVC ≥ 80%), obstructive lung dysfunction (FEV1/FVC < 70 %) and restrictive lung dysfunction (FVC < 80% predicted, FEV1/FVC ≥ 70 %) [24].

Minor Essential Revisions
1. Regarding Reference: authors mentioned references as superscript as well as within second bracket [ 239 lower lung function was associated with a state of insulin resistance, both longitudinally 6 and 240 cross-sectionally [25]- ]

Correction was done

2. Quality of written English is very poor. There are so many grammatical errors in the article. A professional language editing service with native English speaker was used for edition of the manuscript.
3. Table -2 : alignment of the columns should be corrected.

Column alingment of Table2. was corrected.

Level of interest: An article of limited interest
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests