Author's response to reviews

Title: Melasma and its association with different types of nevi in women: A case control study

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Version: 5 Date: 8 May 2008

Author's response to reviews: see over
Dear Editor

Sorry for delay. Thanks to the valuable comments of the reviewers, I revised the manuscript based on the comments of the reviewers. I corrected most of the problems mentioned by reviewers. The point by point responses are as follows. I also added the “competing interests” and “authors’ contributions” sections.

Best regards
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Reviewer1:
1. different types of pigmented lesions have been correlated with the presence of melasma, which include nevi and even lentigines and freckle, which could be different pathogenesis:
OK. We clarified it a bit more in discussion section.
Although our main focus was on melanocytic nevi but there maybe some similarities either. For example association of estrogenic hormones with melasma, lentigens and melanocytic nevi is declared in literature. Also an association of sun exposure with melasma, melanocytic nevi and freckles (in early childhood) is reported to exist. Freckles, melanocytic nevi and lentigens are also considered to have genetic inheritance.

2. the phototype of the individuals in case and control group should be reported.
corrected as recommended by the reviewers. In results

3. since some of the pigmentary lesions evaluated as well as melasma could be dependent on the sun exposure abitudines, these should be reported

Corrected as reviewers had recommended.
189 of the total participants were urban residents mostly housewives or employees living in religious city of Ardabil wearing similar Islamic clothes leaving only the hands and parts of face to be uncovered.
24 of the melasma patients and 27 of the control group participants were rural residents being more exposed to sun in summer and harvest time compared to urban participants but without difference between study groups.

4. the localization of the pigmentary lesions should be described to have the distribution in sun exposed or non-exposed site
regarding locations which due to categorical data entry at the time of conducting study, I can’t provide what was requested. But this although as the respected reviewer has stated could have been quite informative specially if we could do a subgroup analysis in this regard, is not affecting much the main objective of study. We wanted to use the possible
association for prediction purposes and our aim was not to declare any causal inference which a case-control design is not suitable for such an objective. No doubt further research may be needed to clarify the validity and specificities of observed association. But the fact with our manuscript is that this research is the starting point which will motivate other researchers to conduct larger scale prospective studies eliminating the limitations of this study.

5. the number of nevi in the control population seem to be low as compared with previous published data
Explanation provided at the end of second paragraph in discussion section.
The lower mean number of nevi in control group who lack melasma, seems to be mainly due to coincidence or association between melasma and melanocytic nevi, but the general difference of mean number of nevi compared to other studies can be due to other factors like different sun exposure level, different age distribution among study populations and different genetic or hormonal status among studies.

6. few explanations and/or hypothesis on the described association are reported in the discussion
we improved it.
Assuming some common etiologic similarities between nevi and melasma, there seems to be a biologic plausibility to support statistical findings of our study[16] Maybe some common environmental, hormonal or genetic factors play a role in association between melasma and nevi that needs further studies. For example association of estrogenic hormones with melasma, lentigens and melanocytic nevi is declared in literature. Also an association of sun exposure with melasma, melanocytic nevi and freckles (in early childhood) is reported to exist. Freckles, melanocytic nevi and lentigens are also considered to have genetic inheritance. Our main objective of study was to check for possible association between nevi (mainly melanocytic nevi) and melasma to be used for prediction purposes and not to declare a causal relation and we used a method of regression analysis. As we know the concept of regression doesn’t generally imply any causal relation between regressor and regressand[17]. Further research may be needed to clarify the validity and specificities of observed association.

Reviewer 2:
Introduction â## A statement about etiologic similarities between nevi and melasma is made. Are the authors referring to melanocytic nevi? Since the study hypothesis is centered around these similarities, the authors should expand on this issue.
Improved in introduction and discussion.
Yes exactly as the respected reviewer has notified we were focused mainly on melanocytic nevi. There seems to exist an etiologic similarity between melasma and different kinds of nevi, which are considered as genetic factors, hormonal factors and sun exposure. Such similarity is observed more in case of melanocytic nevi and melasma. But although weaker plausibility is assumed for other types of nevi but including them in prediction model improves the prediction which is our main objective of our study. Causality based studies can be conducted later.

Materials and Methods â## The statement concerning the study statistical power
is obscure. Besides the strength of the association, the authors should define the prevalence of the associated condition and, based on the alpha and beta error accepted, they should provide an estimate of the size of the sample to be studied.
Corrected as recommended by the reviewer. 3rd paragraph in methods.

Were hormonal factors, parity and gynecological history considered in the study?
I suspect that skin phenotype may have a role in influencing both melasma and nevi. Was information about skin phenotype and eye and hair color collected in the study?
Some parts are answered and corrected similarly as for the first reviewer’s comments.
Others as follows:
We were determined to exclude participants with known hormonal or ovary related gynecologic diseases but no such a case was encountered during study. We checked for the recent use of ocps and hormonal drugs but in case of life time history of ocp usage as we had not access to health center records we didn’t relay on memory answers and didn’t include it. Data regarding recent use of ocps didn’t show any difference between groups. This maybe due to the fact that some melasma patients know that ocps may cause or aggravate their problem and don’t use it.