

## Peer Review File

Article information: <https://dx.doi.org/10.21037/pm-21-70>

### Reviewer A

**Comment 1:** I enjoyed reading your work and it is well-written. A table summary of the studies mentioned through the text would be beneficial to the readers to follow along with the results. There were quite a few studies mentioned with different associations with AN and I found myself getting lost with the studies. A table would help guide readers and refer back to the studies mentioned for further review. Please also note the term "rate" and "prevalence". Prevalence is mentioned as a rate, which it is not, it is a proportion not a rate. Please refer to prevalence as prevalence and not prevalence rate. A prevalence tells us the proportion of the population has a disease at a given time. A rate, like incidence, tells us when a disease appears and how long those with the disease have it. Please be thorough with your epidemiological terms. I have attached my edits/comments for you.

**Reply 1:** Thank you for these comments. In order to help readers as you suggested, a table with the key studies discussed in the text have been included in a table, highlighting the sample, the variables measured, and results. We have clarified the terminology on line 112. Deleted the word rates from both sentences as advised.

### Reviewer B

**Comment 1:** In line 34, in the Objective, "literature of AN in the pediatric population", should be put "Acanthosis nigricans (AN)". You put the abbreviation just in the Background, on line 38.

**Reply 1:** Has been changed.

**Comment 2:** Include "insulin resistance" before the abbreviation "IR", in line 48, in the Conclusion.

**Reply 2:** Changed.

**Comment 3:** In line 112-115 "Our understanding of this limitation is developing, with growing literature on the relationship between socioeconomic status and structural racism effects on population health", what do you mean by structural racism? I think I would not put this and would not mention this detail in the article.

**Reply 3:** This has been removed from the article

**Comment 4:** In line 337, you should say "Ng et al" and in line 342 "Sayarifard et al"

**Reply 4:** This has been changed as advised.

**Reviewer C:** This is a welcome review of a topic that has not been well covered in the pediatric literature, yet is commonly seen in pediatric practice. It is well written but I would suggest a few additions to make it even more useful.

**Comment 1:** Can the authors describe what is known about the impact of AN on quality

of life or how much it (as opposed to the obesity that is often related) concerns pediatric patients? Appearance is so important but this is not mentioned. If not done, it seems to be an unmet need that should be described.

**Reply 1:** Thank you for this suggestion. A paragraph has been added in the beginning on lines \*\*\* that detail psychosocial consequences of AN and the impact on quality of life of patients. Again this topic is addressed at the beginning of the “Treatment” section.

**Comment 2:** The pathogenesis is briefly mentioned as related to the hyperinsulinemia and receptor stimulation -- is that all that is known? How does this lead to the thickening and darkening with the pattern seen and why in these areas? Any research out there?

**Reply 2:** Thank you for bringing up this point. We have added a section in the dermatologic presentation that goes into more detail regarding the pathogenesis of AN. Several other mediators including FGFR, EGFR, and IGF-1 receptors have been implicated in the role of AN, as well as perspiration and friction that lead to the predilection for intertriginous sites.

**Comment 3:** The authors mention a scoring system, which if simple, might be a good idea for practitioners to use to rate severity. Could that be elaborated upon?

**Reply 3:** Thank you for this suggestion. A table has been added (Table 4) that details the scoring system by Burke et al. Although not widely used, this scoring system is simple and may help predict higher likelihood of insulin resistance (Burke et al, 1999; Choudhary et al, 2017).

**Comment 4:** There is little mention of the syndromes with AN in association other than the mention of increases in FGFR3 in the differential diagnosis. Given that the audience is pediatricians, a table of the genetic disorders could be added

**Reply 4:** A table (Table 2b) has been added that addresses the genetic disorders of FGFR3 mutations associated with AN.

**Comment 5:** On page 9, lines 215-219, there is discussion of a recommendation from the AD, but the reference is from the European Society for Endocrinology/Peds Endocrine Society and has no such information. Could the wrong reference have been cited?

**Reply 5:** Thank you for catching this. The appropriate reference has been cited.

**Comment 6:** On page 35, there is mention of anti-insulin receptor antibodies in autoimmune disorders (SLE, but others too with AN, such as JDM?) -- is this a requirement for the association -- and can we hear more about this? Or is it more likely that these patients with autoimmune disease have hyperinsulinemia (and does it relate more to steroid use or related obesity/metabolic disease or the underlying autoimmune disease itself?

**Reply 6:** Thank you for this suggestion. It is a fascinating topic however we believed it would be too out of scope of this article to elaborate fully on the autoimmune conditions and associations with autoantibodies. We have updated the chart to say “due

to development of insulin receptor antibodies in autoimmune diseases e.g. systemic lupus erythematosus” as this is what has been researched thus far. There are current studies that suggest unknown autoantibodies apart from the insulin receptor antibody may account for the development of AN as well, explaining how cyclosporine has helped patients with regression of AN when they have SLE/Sjogrens. Kondo et al’s paper of autoimmune acanthosis nigricans explains some of these findings. (PMID 22649336)

#### **Reviewer D**

**Comment 1:** It is quite long and seems to lose focus at times. Better if they just concentrated on acanthosis nigricans and leave out the general explanations on insulin resistance, calculating BMI/waist to hip, etc. Much of the biochemical changes reported in acanthosis could be easily summarised in a table.

**Reply 1:** The biochemical changes reported in acanthosis have been limited. Calculation of BMI/WHR has been eliminated from the manuscript, and recommendations for glucose testing has also been limited as to enhance clarity of the manuscript.

**Comment 2:** Please avoid using non-SI abbreviations such as AN and IR. These seldom improve readability, but often generates confusion.

**Reply 2:** We have done this for the simplicity, instead of writing out the full names. We have changed it to remain consistent throughout the text, whereas AN refers to acanthosis nigricans. Insulin resistance has not been abbreviated as suggested.

**Comment 3:** Using first author’s names in the text, rather than just citing the reference, is distracting (eg. Ehsani et al reported .... (60).

**Reply 3:** Thank you for this suggestion. Most of the author’s names have been deleted from the text as to eliminate this distraction.

**Comment 4:** The conclusion in the abstract doesn’t match the rest of the abstract.

**Reply 4:** This has been changed to clarify the key points and match the abstract.

**Comment 5:** What is the rate of acanthosis nigricans in normal weight children/adolescents?

**Reply 5:** This is an important question. Data regarding the prevalence of AN among normal weight children has been added to the section “BMI and Waist Hip Ratio.”

**Comment 6:** The 2nd paragraph of the section ‘Calculation of BMI and Waist to Hip Ratio (lines 143-147) seems out of place

**Reply 6:** This paragraph has been moved and positioned in the first paragraph to better clarify and give example to the previous statement that high BMI, insulin resistance, metabolic syndrome are associated with development of acanthosis nigricans.

**Comment 7:** Oral treatments – etretinate has not been available for 15+ years

**Reply 7:** This treatment has been removed from the article to emphasize the relevance in today's medical management.

**Comment 8:** Summary – this doesn't quite follow the previous discussion, but adds new narratives (eg Family involvement, sleep therapy, etc)

**Reply 8:** Thank you for pointing this out. We have added a section titled "Multidisciplinary Approach" that details the new narratives including family involvement and sleep therapy. Thus we have created a new summary that acts as a conclusion for the manuscript.

**Comment 9:** Images – they are not the best examples of acanthosis.

**Reply 9:** These have been updated as advised.