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IRB proposal

Prevalence of insulin resistance in an immigrant South Asian population with low-normal BMI

1. Study purpose and rationale

The increased cardiovascular risk in South Asian populations has been well documented[1]. Analysis of cardiovascular disease between various ethnic groups has demonstrated that South Asians have a 3-5 fold increase in overall mortality, are prone to developing CAD at a younger age, and are more likely to have multi-vessel disease, left main disease, or distal CAD found on cardiac catheterization[2]. Studies have demonstrated that this increased risk is present in both South Asians living in their native countries, and in immigrant populations (majority of studies conducted in England and Canada)[3,4].

Although the majority of traditional cardiovascular risk factors such as hypertension, hyperlipidemia, and smoking do not appear to contribute to the increased cardiovascular risk seen in South Asians, it has been shown that South Asians have a much higher prevalence of type 2 diabetes mellitus, particularly those living in urban settings and in immigrants to Western countries[1,5]. It is thought that both environmental factors (i.e. diet, affluence) and genetic predisposition contribute to this increased risk.

Obesity is associated with insulin resistance and the development of diabetes, however initial cross-sectional studies indicated that South Asians' increased risk of diabetes was increased despite a similar BMI as their European counterparts[4]. Closer examination of the data revealed that for a similar BMI, South Asians had an increased waist-hip circumference suggesting that their fat distribution was primary abdominal versus subcutaneous. Increased abdominal obesity is one component of the metabolic syndrome, also defined by glucose intolerance, reduced HDL, hypertriglyceridemia, and hypertension, which pre-disposes individuals to both diabetes and increased cardiovascular mortality. Furthermore, the pathophysiologic contribution of increased abdominal adipose tissue to the development of insulin resistance has been well established. These findings have led to an updated definition of obesity in South Asians, with a BMI of >25 now considered obese, and 23-25 considered overweight[6].

These BMI categories are very important, as they are one of the primary tools by which clinicians guide screening for diabetes and initiate preventative measures through diet and lifestyle modifications. In determining these BMI cutoffs, researchers relied primarily on morbidity/mortality outcome measurements and diabetes prevalence. However, studies have been shown that atherogenic changes can occur before diabetes is manifested[7]. Although both insulin resistance and decreased insulin secretion are risk factors for conversion to diabetes, studies have indicated that the increased cardiovascular risk is predominantly in the insulin

resistant pre-diabetic population[8]. Non-diabetic South Asians have relative hyperinsulinemia compared to their Caucasian counterparts, suggesting that the diabetic pathogenesis in this population is primarily a result of insulin sensitivity[1,9]

By using a BMI > 23 as a cutoff, are we missing the chance to initiate primary prevention measures in at-risk South Asians? In this study, I propose to look at insulin resistance in South Asians with a BMI between 19-23 (considered to be normal weight) as compared to their Caucasian counterparts.

As a follow-up study, we propose to look at the proportion of abdominal adipose tissue (i.e. visceral fat) and intrahepatic and intramyocellular lipid accumulation via MRI/MRS. Recent studies indicate that in particular, hepatic fat levels can be correlated with insulin resistance[10]. Preliminary studies looking at the correlation between insulin resistance and visceral fat proportion in South Asians have been largely uninterpretable given the small sample size[11,12]. Although we feel that an understanding of the abdominal fat distribution will help to further elucidate the molecular mechanisms of insulin resistance in South Asians, we will defer this study until we have preliminary results from our primary study given the prohibitive cost of MRI/MRS.

2. Study design and statistical analysis

This study will recruit South Asians and Caucasians between the ages of 18-35 and classify them into three groups based on their BMI (19-21, 21-23, and 23-25). Patients will then have their insulin resistance determined by calculating a QUICKI score based on fasting insulin and glucose levels. Insulin resistance will be defined as a QUICKI score < .33[13].

To determine significance, we will used a chi squared test with the proportion of insulin resistance as the independent variable.

Studies have shown that ~ 31.8% of the non-diabetic general population has insulin resistance[14]. We can thus predict that the prevalence of IR in the South Asian non-diabetic BMI 23-25 group would be significantly higher than that number (especially since the general population of South Asians has an 18% prevalence of type 2 diabetes). We can thus estimate the prevalence of IR in this population to be ~ 40%. Within the Caucasian subgroup, as a BMI of 23-25 is considered normal, we would expect the prevalence of insulin resistance to be closer to that of the general population (i.e. 30%). In the BMI 19-21 and 21-23 groups, we would expect the prevalence to be much lower for both South Asians and Caucasians.

To detect a clinically significant difference (i.e. one that would prompt a clinician to change their screening process), one can hypothesize that a 10% difference in the rate of insulin resistance would be needed to justify treating this population differently in terms of costly screening tests. Studies have shown that anywhere from 10-30% of patients with insulin resistance convert to type 2 diabetes over a 7 year period[8]. If we hypothesize that the South Asian BMI 21-23 group has an IR

prevalence of 20%, we would need ~ 219 participants in each category to detect a clinically significant difference. If we hypothesize that the South Asian BMI 19-21 group has an IR prevalence of 15%, we would need ~ 160 participants in each group.

3. Study procedures

Once the patient has been deemed eligible for participation in this study, he or she will report to the outpatient clinic site to undergo BMI determination via height and weight, and classification into the appropriate category.

In order to determine the prevalence of insulin resistance in each category, we will utilize the QUICKI model, which uses the fasting glucose and fasting insulin to approximate insulin resistance. This model has been shown to correlate well with the hyperinsulinemic eugycemic clamp method, which is the gold standard for accurately determining insulin resistance, but is time intensive and cannot be practically implemented in a large study[15].

Measurement of QUICKI = $1/[\log (I(0)) + \log (G(0))]$ where I(0) = fasting insulin and G(0) = fasting glucose. A QUICKI score of < .33 (75% cutoff) has been used to define the presence of insulin resistance[13].

4. Study drugs or devices

N/A

5. Study questionnaires

N/A

6. Study subjects

Subjects between the ages of 18-35 will be identified for recruitment through flyers posted at major medical centers and universities within New York City. South Asians will be classified as having familial origins in India, Pakistan, or Bangladesh. Both US-born and immigrant South Asians will be accepted into the study. Patients will be excluded if they have a known diagnosis of diabetes. Other exclusion criteria will be known cardiovascular disease or MI, concurrent use of medications that can affect insulin resistance (i.e. steroids). Patients will be screened for participation eligibility through a phone interview conducted by a study coordinator.

7. Confidentiality of study data

Study participants will be identified with a unique identifier number, and their data will be stored with appropriate encryption and security mechanisms. Access to study results will be limited to investigators directly involved in the study. Results of blood work and imaging will be made available to the individual participant.

8. Conflict of interest

The study investigators report no potential conflicts of interest.

9. Location of study

The study will be conducted at Columbia University Medical Center, in concordance with all institutional policies.

11. Potential Risks

The only procedure that patient will undergo is a venipuncture for blood sampling. This procedure is minimally invasive, with risks including bleeding, hematoma, infection.

12. Potential Benefits

Any participant found to have insulin resistance (or overt diabetes) will be informed of these results and referred to a primary care physician for counseling and appropriate medical intervention as indicated.

13. Alternative Therapies

No treatment is proposed in this study.

14. Compensation to subjects

Subjects will be compensated $50 for participation in this study.

15. Cost to subjects

None

16. Minors as research subjects

N/A

17. Radiation or radioactive substances

N/A

18. References

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