Obesity and Diabetes Research Group : Bellville South Africa Study and other studies

Past, present and future

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Chemical Pathology

Background

- Study started in 2005 in collaboration with CPUT.
- Examined children for the presence of diabetes, obesity, hypertension and metabolic syndrome
- Expanded in 2008 to include adults and consists of 3 divisions : epidemiology,clinical and molecualar and cell based studies
- Bellville South Africa Study and falls under the epidemiology group
- Clinical studies on MODY and Acanthosis Nigrans led by Dr Hoffman (in collaboration with Prof Hough and team
- Molecular and cellular based studies led by Dr Ali: examining the role of vitamin D and fat accumulation as well as the role of adipponectin in weight loss (Dr Ferris)

Students

Doctoral

- Yandi Yako
- David Soita
- Macharia Muiruri
- Zelda Vergotine (staff)
- Dr Annie Zemlin (staff)
- Dr M Hoffman(staff)
- Shafick Hassan (staff)

Masters and honours

- Botumela Fanampe
- Avril Somers
- Emmanuel Bahta
- Soso Ngamso
- Maria Hartnick
- Tjoranda Timothy
- Clare Bartel
- Yogan Kisten
- Grace Kiraka
- ClaresSpringhorn
- Baaghith Amul
- Dr Abid
- Rafeeah Kaskar

Members

- Cape Peninsula University of Technology

Prof Matsha , Mr Hassan

- University of W Cape

Dr Sue Bassett and Ms Clare Bartel

- University of Stellenbosch

Prof Essop

- University of North West

Prof Salom Kruger

- Aga Khan University, Kenya

Prof Ojwang

- Medical Research Council

Dr Andre Kengne and Dr Liz van der Merwe, Pathology

Prof Kotze, Prof van Rensburg ,Dr Rensburg and Dr Ali

Bellville South Africa Study

- Established in 2008
- Focus on CVD risk factors since CVD is the leading cause of death after HIV/AIDS
- Particularly focused on diabetes,metabolic syndrome and CKD as they are independent risk factors for CVD.
- We chose to study the mixed ancestory population as they constitute nearly 55% of W Cape and have been shown to have the 2nd highest prevalence of diabetes in South Africa after the Indian population

What is the extent of the problem?

- We examined the prevalence of diabetes, metabolic syndrome and chronic kidney disease all of which are known risk factors for CVD in a well defined (adult) urban and stable community of Bellville South (941 subjects)
- Our hypothesis was that due to urbanization and altered criteria for diabetes diagnosis there would be an increase since the last survey carried out in 1996/1997 (Levitt et al,1999) which used WHO 1985 criteria
- Determine the life time CVD risk using a risk calculator
- Use non traditional markers of CVD risk such as anti-oxidised LDL

Bellville South Community

- Established more than 30 years ago
- 95% mixed ancestory
- Lower to middle income
- Total population of approximately 25,000 of which 6500 between 35-65 years
- Stable

Results (cross sectional)

- Age adjusted prevalence of 33.5% (OGTT)
  95% CI 30.0 – 36.9%)
- Age adjusted IGT was 13.6 % (95% 11.0- 16.1%)
- Undiagnosed diabetes (age adjusted) was 12.4% (95% CI 9.8 - 14.8%) – more than half of the total number were not aware of their status
- Metabolic syndrome 46.5 % (JIS criteria) with higher rates in females
- Central obesity was almost 3 times higher (72.4%) in females than males (25.6%) and was the most common component in females regardless of the cut off (88 cm)
- Life time CVD risk in known diabetes was 60% and without diabetes, 33.6%. High risk scores were observed in normoglycaemic individuals

Results (2)

- Major predictors were sibling history of diabetes, Trigs, LDL-C and HbAIC levels
- Low levels of anti-oxidised LDL in hyperglycaemic subjects with high CVD risk scores suggesting in vivo LDL oxidation
- Surprisingly , a high prevalence of CKD of 26% (irrespective of glycaemic status)

Assessed the phenotypes that were associated with progression to diabetes

- 333 subjects whose glycaemic status was known at baseline were followed up and at 3 years a repeat OGTT carried out in 198 subjects (after excluding known and newly diagnosed diabetics)
- HbAIC, HDL-C, DBP and Metabolic syndrome were major determinants of progression to diabetes and NOT BMI or waist circumference which may have implications for screening and prevention strategies

Are polymorphisms in specific genes associated with diabetes/IR and CKD as reported in other population groups

- Investigated the distribution of Pro12Ala, a polymorphism in PPARγ gene that promotes insulin sensitivity and found a similar distribution between normo and hyperglycaemic subjects
- Similarly 3 SNPs in the MYH gene that had been reported to be a risk factor of CKD in Afro Americans were not found to be associated with CK (now reported to be a hitchhiker gene)
- Currently examining the association between APO L1 polymorphisms and CKD as this is located on the same loci as MYO gene and has been reported to have a much higher odds ratio (>5)
- Important to note that in both reports the protein expressed by these genes has not been identified

Can HbAIC be used to screen asymptomatic subjects for diabetes ?

- Recently, ADA and other organizations recommended that HbAIC can be used for detecting subjects with diabetes and suggested a cut off value of 6.5%
- We have provided evidence that in this population group a level of 6.1 % is more appropriate
- Assess the value of Glyc N Acylation of target proteins on WBC's for the diagnosis of diabetes and IGT
- a novel molecular-based assay that will allow for the earlier detection of pre- and overt diabetes.
- Hypothesized that with pre-diabetes there is increased flux through the hexosamine biosynthetic pathway that leads to greater post-translational modification ("O-GlcNAcylation") of target proteins in white blood cells and the degree of O-GlcNAcylation increases in parallel with higher fasting blood glucose levels (in collaboration with Prof Essop)
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Obesity and Metabolic syndrome in Schoolchildren

- In a study of more than 1222 children we established that school learners have one of highest prevalence of obesity and the metabolic syndrome in Africa
- Observed that Mmetabolic syndrome may be present in normal weight children
- hsCRP, a CVD risk marker was found to be strongly mediated by waist circumference and obesity and exceeded 3 mg/L in 19% of children – indicating that young South African children are already at risk for developing CVD
- Found that polymorphisms in genes regulating the leptin melanocortin pathway MC3R (an energy regulating melanocortin receptor) may have a protective effect on weight and blood pressure in children of mixed ancestory
- Whilst others such such as CART was associated with obesity susceptibility

Conclusion

- Subjects from a mixed ancestory background are at an increased risk of diabetes and CVD and thus should be encouraged to know their glycaemic status
- HbAIC levels may be used as marker of CVD risk and progression to diabetes
- Many subjects are unaware of their diabetics status
- Both obesity and metabolic syndrome in both children and adults are among the highest in Africa
- hs CRP may be used to identify high risk children
- HbAIC levels of 6.5 % cannot be used to screen for diabetes as suugested by WHO and ADA

Recent Publications

Matsha T, Hassan S, Bhata A, et al. Metabolic syndrome in 10-16-year-old learners from the Western Cape, South Africa: Comparison of the NCEP ATP III and IDF criteria. Atherosclerosis 2009;205(2):363-365.

Yako Y, B L. Fanampe, S Hassan, R Erasmus, L van der Merwe, T Matsha (2011).Negative association of MC3R variants with weight and blood pressure in Cape Town pupils aged 11-16 years, SAMJ , 6, 35-39

Matsha T, B Fanampe, Y Yako, S Hassan, M Hoffmann, L Van der Merwe, RT Erasmus (2010) Association of the ENPP1 rs997509 polymorphism with obesity in South African mixed ancestry learners E Afr Med J, 87 No. 8 , 35-40

Zemlin A, Matsha T, Hassan M, Erasmus (2011) .HbAIC of 6.5% to diagnose Diabetes – The Bellville South Africa Study. PloS ONE, 6: 2258-2261.

Yako Y , Hassan S, Van der Merwe L, Erasmus R, Van Rensburg S, Matsha T (2011) Association of cocaine and amphetamine , leptin and leptin receptor gene polymorphism with anthropometric obesity phenotype indicators in S African learners. J Nutrigenet Nutrigenomics 4, 210-21

Matsha T, Hassan S Kidd M, Erasmus R (2012). The cardiovascular risk profile of S Africans with diagnosed diabetes, undiagnosed pre-diabetes or normoglcaemia: the Bellville South Africa Study. Cardiovascular J of Africa, 23, 1, 26-30

Yako Y, Hassan M, Van der Merwe E, Erasmus RT, Matsha T (2012) Associations of MC3R polymorphisms with physical activity in South African adolescents. J Physical Activity and Health, *In press*

Rensburg M, Hassan M, Matsha T, Erasmus R (2012 Distribution of hCRP and its association with cardiovascular risk variables of metabolic syndrome in S African learners, J ASLM, *In press*

Matsha T , TjorandaT, Hon D, Hasan S, Erasmusr R(2012). Antibodies against oxidised LDL and cardiovascular risk factors in individuals with hyperglycaemia S Afr J Diabetes & Vasc Dis, *In press*

Future Plans and Studies

- Expand current population base to 5000
- Extend prospective study to 10 years
- Develop e-based intervention tools
- Collaborate with S African Diabetes Assoiction and MRC to promote diabetes self testing in mixed ancestory population (know your diabetes status)
- Develop prediction modelling tools that are user friendly

Family/genetic studies

- Investigate the association between family (parental) history of obesity, hypertension, and diabetes (metabolic syndrome traits) and the presence of the metabolic syndrome (MetS) in offspring in the Bellville South (BS) community (across 3 generations).

Family studies

- Is the incidence of MetS higher in individuals with a positive family history of MetS (obesity, hypertension, and diabetes) compared to those with no history?
- Does the magnitude of the increased risk vary according to the components of the syndrome present in the parent?
- Can parental history of MetS reliably predict the syndrome in the offspring?

Examine the role of paraoxonase in mediating LDL peroxidation

HDL -c is an anti-oxidant and prevents LDL oxidation by a mechanism that is mediated by paraoxonase 1 (PON1)

- Assess the distribution of common PON1 genotype (Q192R & L55M) and phenotype (activity & levels)
- How does PON1 modify serum apolipoproteins, LDL and HDL cholesterol levels and size and impact on the risk/severity of atherosclerosis as reflected by carotid artery IMT

Biomarkers to assess cardiovascular risk and detection of diabetes

- To examine the association of HbA1c levels with risk of the MS in a community based setting and determine cut-off values in the diagnosis of MS
- To examine the association of HbA1c levels with future clinical cardiovascular events in a community based setting and to determine what level of HbA1c is predictive
- To investigate if HbA1c can be used as a marker of future cardiovascular risk in association with traditional biochemical cardiovascular risk predictors (troponin I and hs-CRP) and future biochemical markers of cardiovascular risk (adiponectin and E-selectin)