BSPED Research and Innovation Award 2019 Final Report

CoMBAT Study
Clinical effects of Metformin on Bones in Adults with Type 1 diabetes mellitus (T1DM)

Background Adults and children with T1DM have impaired bone health with poorer bone microarchitecture[1,2] and a significantly increased fracture risk compared to the general population and those with Type 2 diabetes mellitus (T2DM)[3,4]. Reduction in fracture risks has been noted in T2DM patients on the anti-diabetic drug metformin suggesting a bone protective effect[5,6]. In vitro studies during my MD demonstrated that metformin may exert its bone protective role by promoting osteogenesis and suppressing adipogenesis[7]. We aimed to investigate whether metformin treatment improved bone formation, in adults with Type 1 diabetes mellitus (T1DM) compared to the placebo group.

Methods Age, sex and BMI-matched bio-banked plasma and serum samples from adults with long-standing T1DM, randomised to oral metformin 1000mg twice daily or placebo in the REMOVAL study[8]; an international multicentre, double-blind, placebo-controlled trial; were retrieved from the NHS GGC Biorepository. Markers of bone formation, bone alkaline phosphatase (BAP), and bone resorption, tartrate-resistant acid phosphotase (TRAP) 5b, were analysed at randomisation immediately prior to study treatment, and 3 years after. Sclerostin, the inhibitor of bone formation, which has been shown to predict fractures in T1DM were also assayed, together with parathyroid hormone and 25-hydroxyvitamin D. The primary outcome was BAP levels comparing the two arms whilst secondary outcomes include TRAP5b and sclerostin levels.

Results Ninety-six patients with a median age of 55.8 (41.1,73.5) and 55.8 (40.8,75.6) in the metformin and placebo arms respectively, were recruited with 48 (32M:16F) in each group. The groups were comparable for methods of insulin delivery, diabetes duration [metformin 29.5 (14.2,63.6) vs placebo 34 (10.8, 51) in years], HbA1c at baseline [metformin 64 (48,85) vs placebo 63 (54,78) in mmol/mol] and at 3 years [metformin 65 (45,86) vs placebo 63 (49,85) in mmol/mol]. BAP level rose in the metformin group with median BAP (mcg/l) of 16.6 (6.3,44.4) and 19.6 (0,41.3), pre- and post-treatment respectively. This was not statistically significant (p=0.103) when compared to the median BAP (mcg/l) of 15.9 (1.9, 34.6) and 22.1 (10.1,44.1) in the placebo group, pre- and post-treatment respectively. TRAP5b was statistically significant (p<0.042) between the groups for metformin [pre 3.03 (1.66, 5.93); post 3.07 (0.06,5.52)] and placebo [3.35 (0.03, 6.55), post 3.57 (1.07,7.23)].

Conclusions Our results showed that in adults with T1DM, metformin may have a beneficial role in bone health by suppressing the age-related bone resorption, with minimal effect on bone formation.

Manuscript in preparation with BSPED acknowledgment

Benefits to Applicant

The BSPED Research and Innovation Award has had a tremendous impact on both, my professional and personal development. Armed with the award, it enabled me to competitively secure the Chief Scientist Office National Research Scotland (NRS) Career Research Fellowship in early 2020, which provided me protected time within the NHS for academic work. More specifically, the award funded the 'Clinical effects of metformin on bones in young adults with Type 1 diabetes mellitus' (CoMBAT) study, allowing me to further my MD translational research study on the bone microarchitecture of children with Type 1 diabetes and the therapeutic potentials of metformin for diabetic osteopathy using murine mesenchymal stem cells.

Through the CoMBAT study, I was able to build on my existing collaboration with the Developmental Endocrinology Research Group in Glasgow led by Prof Ahmed and develop stronger links with adult Diabetology via Prof Petrie, Professor of Diabetic Medicine at the University of Glasgow. Both are established mentors with excellent track records in large multicentre trials as well as maintenance and interrogation of large datasets. The CoMBAT study accorded me my first biobank research experience involving a large international multicentre, double-blind, placebo-controlled cohort. Most importantly, the networking opportunity enabled me to eventually secure a Consultant Paediatric Endocrinology post in Glasgow in 2022.

On a more personal level, this award has taught me resilience and perseverance. It took many years to come to fruition following many setbacks – from the unprecedented coronavirus pandemic in 2020 and 2021 with laboratory closures, through to the reliance on other team players in a piggy-back study, and the logistical minefield of data access and analysis in the Scottish National Safe Haven[9] (where data cannot be downloaded or extracted from, and must be analysed in a single location within the highly secure trusted research environment) as well as biochemical assay failure.

Benefits to Institution

I secured the award when I was a Consultant Paediatrician in a DGH. This award brought in valuable research funding to the Health Board and reignited the paucity of research within the Paediatrics Department locally in Forth Valley Children's Hospital. When I took up post in Glasgow in 2022, I transferred this award together with my NRS fellowship to my new institution, the Royal Hospital for Children Glasgow. I now contribute actively to the Developmental Endocrinology Research Group with teaching and research rounds and am actively involved in the Office for Rare Conditions in Glasgow, working on establishing an international registry for novel therapies in rare bone and endocrine conditions (GloBE-Reg). This award has been a true stepping stone to my current involvement as Principal Investigators and sub-Investigators in many other research trials in my institution.

Benefits to Endocrinology

The strength of the CoMBAT study is the randomised controlled cohort of metformin versus placebo in T1DM patients. To date, this remains the only clinical study looking at the benefits of metformin on bone health in T1DM. The findings from the CoMBAT study is consistent with the findings from animal studies[10], suggesting that metformin protects bone health by suppressing bone resorption and stimulating bone formation. There is a need to better understand why children and adults with T1DM fracture more than the general population, as well as those with T2DM. Metformin is increasingly used in T1DM to reduce insulin requirement and also confers some cardiovascular benefits[8], an additional bone protective role would indeed be conveniently advantageous given that this potential therapeutic drug is cheap, safe and well-established.

(986 words)

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