UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE
MEDICAL STUDENT SUMMER RESEARCH FELLOWSHIP APPLICATION

Application Deadline is Friday, March ##, 2####

I. STUDENT INFORMATION

Name: Mark Anthony Griffiths
Email Address: griffimk@ucmail.uc.edu

Address: Phone #:

Social Security #: Birth Date: 06/23/1980

Race: White ☒ African American ☐
Hispanic ☐ Asian ☐ American Indian ☐
Pacific Islander ☐ Other ☐

Education (begin with baccalaureate):

<table>
<thead>
<tr>
<th>Institution &amp; location</th>
<th>Degree, year</th>
<th>Major</th>
<th>GPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yale University, New Haven, CT, USA</td>
<td>B.S. 2002</td>
<td>Biomedical Engineering</td>
<td>3.34</td>
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</tbody>
</table>

MCAT Score: 28

Honors & Awards:
Science and Technology Research Scholar - Yale College - 1998, 1999

Major Career Interests:
My career interests include the specialties pediatrics, pediatric cardiology and orthopaedic surgery.
Describe any research and/or professional experience; list any abstracts or publications.

1/02 - 5/02 "Vascular Flow Mechanics," - Advisor: Prof. Kailasnath Purushothaman - Yale University Department of Mechanical Engineering

My senior project was a biomechanical engineering endeavor designed to identify a better index of myocardial viability than what is currently used. Presently, such evaluations include subjecting an individual to a stress test and measuring the tracer uptake activity. In this project, I proposed the idea that such measurements were inaccurate as there are diffusion limitations and permeability limitations at high flow values. It was further proposed that a better indicator of heart viability would be the permeability surface product. The project covered the field of biomechanical engineering and included mathematical postulates and computer programming using MATLAB.
II. RESEARCH PROPOSAL:
Use the following format. Your proposal should be at least 3, but not more than 5, pages, single-spaced.
(Type in the shaded areas. The space will expand as needed.)

Title
Cross Sectional Study Of Bone Mineral Density (BMD) In Children Exposed To Chronic Corticosteroid Therapy

Background & Significance
Osteoporosis or osteopenia and associated fractures are a serious complication of glucocorticoid therapy when given for prolonged periods at doses exceeding physiologic amounts. Glucocorticoids are known to have direct deleterious effects on bone with their most profound effects during the first months of exposure. They are known to increase osteoclastic activity concurrent with reductions in osteoblastic function thereby enhancing bone loss with reduced bone accretion. Indirect effects on the bone include the 1) development of myopathy with muscle weakness with resultant reduction in the stress on the skeleton with glucocorticoid exposure, 2) decreased calcium and phosphate absorption resulting in secondary increases in PTH secretion, 3) reduced adrenal and gonadal glucocorticoid production with altered estrogen and androgen secretion, and 4) inhibition of type 1 collagen and non-collagenous proteins. Finally, the inflammatory condition for which glucocorticoids (inflammatory bowel disease, chronic kidney disease, asthma, rheumatoid arthritis, autoimmune hepatitis) may also contribute to the bone disease associated with glucocorticoid exposure. This has been shown quite elegantly in studies in adults (1). Glucocorticoid exposure is a known risk for bone disease in adults and is one of the ICD-9CM codes that provides the largest reimbursement for DXA measurement. Very little is known about the short or long term impact of glucocorticoid exposure in children. There are a variety of conditions for which corticosteroids are prescribed. Cross sectional studies in patients with Crohn’s Disease and cystic fibrosis have demonstrated that there is a negative correlation between glucocorticoid exposure and BMD Z-score (2-5). Efforts were not undertaken to determine activity or calcium intake in the subjects from these studies although serum 25-OH vitamin D was reduced in cystic fibrosis (4,5). Whether adequate calcium intake, normalization of vitamin D status or exercise are likely to ameliorate the deleterious effects of glucocorticoids on bone is unknown.

There is now a substantial body of evidence that bisphosphonates are effective in the treatment of postmenopausal osteoporosis, Paget's disease, corticosteroid induced bone loss, and osteogenesis imperfecta (6-9). Currently, bisphosphonates, including alendronate and risedronate, are approved by the FDA for treatment of Paget’s Disease and postmenopausal osteoporosis and glucocorticoid-induced osteoporosis. Both are comparably effective in the improvement of bone density in affected populations (10-15). Both agents have been demonstrated to be effective for the management of glucocorticoid induced osteoporosis (14-16). Recent studies have demonstrated the effectiveness of bisphosphonates for the treatment of glucocorticoid induced osteoporosis. In a metaanalysis of 13 controlled trials including adults receiving a means steroid dose of 7.5 mg/day or more, Homik et al found that 1 year of treatment with bisphosphonates (including etidronate, risedronate, alendronate and pamidronate) leads to a different of 4% in lumbar spine BMD between treated and control subjects (17). Despite a 24% reduction in vertebral fractures between treated and placebo subjects, this difference did not reach statistical significance. In adults receiving 7.5 mg/day of prednisone, risedronate increased BMD by 2.9% at the lumbar spine compared to no change in BMD in the control group. There was a 70% reduction in vertebral fracture rate in the treated v. placebo treated groups with no associated upper gastrointestinal adverse events (16).
Pamidronate has been approved for treatment of hypercalcemia of malignancy, Paget’s Disease, and osteolytic bony metastases. Little experience has been reported in children; however, these agents are being used with more regularity in children without specific data regarding their safety or efficacy. The largest published experience using pamidronate has been in the treatment of osteogenesis imperfecta (8,18) and for juvenile osteoporosis (19). Recently, a single center uncontrolled trial of pamidronate treatment of non-ambulatory children with cerebral palsy demonstrated its benefit for this patient population (20). One large multicenter study has been reported evaluating the efficacy and safety of alendronate for treatment of osteopenia in children with connective tissue disorders (21). Using alendronate at doses of 5 mg for subjects < 20 kg and 10 mg for those > 20 kg, lumbar spine BMD increased significantly from baseline in 38 treated patients compared to untreated who had only a modest increase in bone mass over a 1 year period. Of this patient population, 33 of 38 subjects receiving alendronate had either previous or concurrent corticosteroid treatment. Generally, the drug was well tolerated with only 1 subject developing esophageal erosions that regressed with cessation of treatment. Bisphosphonates have been used on a very limited basis in children treated with glucocorticoids. In an uncontrolled trial of intravenous alendronate in 4 girls on glucocorticoid therapy, Falci et al found a 114% increase in lumbar spine BMD after 12 months (22). A subsequent study from the same group, reported as an abstract, demonstrated significant increase in LS BMD after 6 months therapy in 46 glucocorticoid-treated children with rheumatologic diseases, age 5-18 years, whose initial BMD Z scores were more than –2.0 at enrollment (23).

My mentor has had a research interest in bone disease that began in 1976. Most recently, he has completed a cross-sectional study of lumbar spine BMD in non-ambulatory children and adults and the PI and CoI have initiated a double blind placebo controlled trial of risedronate for the treatment of bone disease in this population which has now enrolled more than 21 subjects with follow up of from 6-12 months. He has also recently completed a cross sectional study of bone density in patients after liver transplant and he is a center coinvestigator for the NIH funded prospective study "Bone Mineral Density in Childhood Study" (PI H. Kalkwarf) in which the food frequency and exercise questionnaires are utilized that have been proposed to be used for this study.

There is no previous experience among the investigators for the current proposal and the systematic study of the effects of glucocorticoids on bone. In clinical practice, my mentor has utilized both calcitonin and bisphosphonates for the treatment of osteopenia after liver transplantation and bisphosphonates with inflammatory bowel disease and in cystic fibrosis.

**Hypothesis to be tested**

The hypothesis to be tested in this proposal is that children exposed high dose glucocorticoids equivalent to >5 mg/day of prednisone for 6 months or longer will have reduced bone density compared to age-matched, gender matched controls.

**Specific Aims**

The specific aim of this proposal is perform a cross sectional study lumbar spine dual x-ray absorptiometry (DXA) in 50 children, age 4 years to 18 years with a variety of diagnoses who have had glucocorticoid exposure equivalent to 5 mg/day of prednisone for at least 6 months. The overall goal of this proposal is to determine whether glucocorticoid-induced bone loss in children represents a significant problem for which intervention with bisphosphonates might be appropriate.

**Methods**
To evaluate the prevalence of reduced lumbar spine in children exposed to chronic corticosteroids, we will recruit from multiple clinics of the Children’s Hospital. We will perform a single DXA scan of the lumbar spine, collect information by questionnaire relating to the patient’s chronic disease, and obtain consent to review the patient’s medical record. The study will be conducted at the General Clinical Research Center Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio. Study subjects will be recruited from the medical clinics of the Children’s Hospital Medical Center. Subjects will be between 4 and 18 years old who have been treated with glucocorticoids equivalent to 5 mg/day prednisone for at least 6 months with treatment that is either ongoing or completed less than 6 months prior to enrollment.

Various imaging studies will be employed in this study, specifically, Bone Mineral Content/Density and Plain X-ray studies. BMD of the lumbar spine will be performed using the Hologic Dual Energy x-ray Absorptiometer (DEXA, Hologic 4500A, Waltham, MA) DEXA has become increasingly popular in the measurement of the total body bone mass and found to have high accuracy, and to be precise and sensitive in populations of all ages. We have focused on lumbar bone density measurement as an outcome measure, and have based power calculations on it, because i) lumbar spine BMD correlates highly with BMD at other sites ii) lumbar spine is the only site for which normative data is available. To ensure uniform acquisition of data, the low-density software will be used to analyze all bone density/content measurements for subjects less than 20 kg with an appropriate correction for use of this software. Radiographs of the hand will be performed to assess bone age in case subjects are growth retarded in case an adjustment needs to be made for bone age when assessing DXA vs. controls. Single anteroposterior views of the hand and wrist will be obtained with subjects wearing a lead apron to minimize radiation exposure during the examination. Films will be read by the radiology staff of CHMC. All females above age 9 will have pregnancy tests prior to any X-ray or DEXA studies.

Serum 25-OH vitamin D will be measured in serum (0.5 mL) using the Dia Sorin 25-OH-D (Stillwater, MN) assay that consists of a two step procedure. The first procedure involves a rapid extraction of 25-OH-D and other hydroxylated metabolites from serum or plasma with acetonitrile. Following extraction, the treated sample is then assayed using an equilibrium radioimmunoassay (RIA). The adult reference range is 9.0 – 37.6 ng/mL (n=44). The within-run is 12.5 % CV and the total imprecision is 11.0% CV. The sensitivity of the assay is 1.5 ng/mL; with a crossreactivity of 100% for 25-OH-D2, 25-OH-D3, 24,25-OH-D2, 24,25-OH-D3, 25,26-OH-D2, and 25,26-OH-D3.

Lastly, a questionnaire will be administered to each subject/parent/guardian which will include information regarding demographics (age, date of birth, gender, race, age at menarche [if applicable]), medical condition (primary diagnosis, secondary diagnoses, medications, surgeries), glucocorticoid therapy (onset, dosing, duration). N.B.: Some of this data will be retrieved from the patient's medical record and specific consent will be sought for this within the informed consent document. Patients above age 8 will be asked to complete the pubertal stage assessment using standardized cartoons which has a high correlation with direct inspection (23,24)

a. Food frequency Questionnaire: We will also administer the calcium food frequency questionnaire which is a modification of the food frequency questionnaire developed by Block Dietary Data Systems (Berkeley, CA) and a modification of the Kid’s Questionnaire. This questionnaire is being utilized by the NIH funded Bone Mineral Density in Childhood Study (BMDCS) and approved by the CHMCC IRB. The questionnaire takes about 20 minutes to complete.

b. Physical Activity Assessment: We will assess weight-bearing activity using the self-report tool of Slemenda et al (25). This assessment is similarly being utilized for the BMDCS and has been approved by the CHMCC IRB. This questionnaire requires about 10 minutes to complete.

Plans for Data Analysis, Possible Results and Interpretations
Data analysis will begin by examining descriptive statistics of each outcome variable. The descriptive statistics will include means, standard deviations, minimums, maximums, and normality tests as appropriate. If the outcome variables are not normally distributed, transformations will be made for analysis and the transformed values used.

Comparisons between Z-scores in study subjects and norms will be performed by descriptive methods. Correlations with cumulative glucocorticoid dosage, duration and Z-score using least square linear regression.

This is a cross sectional analysis of a subject population to assess prevalence of reduced bone density, defined as a Z score greater than −2.0. As such no sample size calculation is provided with the proposed enrollment of 50 in this “pilot” study.

If the results of the current study demonstrate a significant reduction in lumbar spine BMD compared to age/sex matched controls, a subsequent treatment trial with once weekly dosing of a bisphosphonate will be considered.

References
III. MENTOR PORTION OF APPLICATION

Name: James E. Heubi, M.D.  Dept.: Gastroenterology
Phone: (513) 636-8046  Email: james.heubi@chmcc.org

TRAINING ENVIRONMENT: Describe the nature and frequency of your planned, direct interaction with the student. Identify individuals who will participate in the student's technical and scientific training. Describe conferences and lab meetings the student will attend. Describe the facilities and resources available for the proposed project in your lab or elsewhere. (The space expands as needed; use up to 1.5 pages.)

At the beginning of the summer session, Mark Griffiths will meet with me on a daily or more frequent basis. He will be oriented to the resources of the GCRC and its staff as well as the Children’s Hospital. Initial interactions will be directed at the mechanics of completing the protocol, recruiting techniques, techniques in completing the planned questionnaires. He will watch the 2-hour videotape on Human Subject Protection required by the IRB at the Children’s Hospital. Weekly meetings will be conducted with Mark and appropriate coordinating staff to determine the enrollment rates and to identify any problems that have developed in the completion of the project. In addition to myself, it is anticipated that Mark will interact with Andre Hawkins, the study coordinator from the Division of Pediatric Gastroenterology and Nutrition; Donna Buckley, the GCRC Body Composition Core Supervisor; Valeria Cohran, a research fellow in Pediatric Gastroenterology and Nutrition; and Kristen Buschle, a research nurse for the GCRC. As the study progresses, it is anticipated that Mark will meet with Cathy McGraw, Supervisor of the Informatics Core of the GCRC for database development and Judy Bean, GCRC Biostatistician regarding techniques of data analysis. If I am not immediately available to answer questions that Mark has regarding the research project, there are ample other personnel available to help. Andre Hawkins will assist with issues of general protocol execution as well as Kristen Buschle. Donna Buckley will assist with issues relating to the DXA.

Mark will participate in a weekly research meeting, which will include specific discussions about his research project. In addition, the student will be provided the opportunity to attend Pediatric Grand Rounds which meets weekly and the weekly Gastroenterology and Nutrition conferences, which meet on 2-3 occasions during the week. Opportunities will be available to attend my one half day/week clinic, which will provide the chance to see some general gastrointestinal disease. Mark has expressed a specific interest in bone disease and orthopaedics. Pursuant this interest, I have had discussions with Charles Melman, D.O, a Pediatric Orthopedist, who will provide opportunities for the student to attend orthopedic clinic. He will also be encouraged to participate in all activities coordinated for the students in the MSSRP.

Mark will recruit his subjects from the specialty clinics of the Cincinnati Children’s Hospital. Data will be obtained from the subspecialty charts for inclusion in the database for this project. Subjects will come to the GCRC at Children’s Hospital where they will have questionnaires administered, blood drawn by the nursing staff and DXA measurements made by the technical staff of the Body Composition Core. The GCRC is now located on A3 of the new portion of Children’s Hospital and has 13,000 square feet including 12 inpatient rooms, 12 outpatient exam rooms, 2 treatment rooms, a preparatory laboratory, a small kitchen, the Body Composition Core (DXA and pQCT equipment) and offices for the Informatics Core Supervisor, the Bionutritionist and her staff, and nursing personnel. Deck space and computer access will be made available for Mark on the GCRC. The Biochemistry Core, where the vitamin D measurements and bone markers are measured is located in B4, which is in the building adjacent but directly connected to the building where the GCRC is located. The Biochemistry Core includes all the required equipment and personnel to provide the analyses planned in the current proposal.
If the proposed project involves radioisotopes, vertebrate animals, or human subjects or material; provide the following relevant information. **Pending authorizations must be approved by April 30, 2022.**

Radiation Safety

Authorized User: _____

Institutional Animal Care and Use:

Institutional Review Board

Principle Investigator: James Heubi, M.D.

Title of IRB Protocol: Cross Sectional Study of Bone Mineral Density in Children Exposed to Chronic Corticosteroid Therapy.