SICKLE CELL TRAIT: A SUB-CLINICAL DISORDER?

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OBJECTIVES

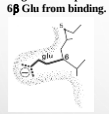
- 1. BRIEFLY REVIEW SICKLE CELL DISEASE
- 2. DISCUSS THE HISTORY OF SCT AND THE SURROUNDING CONTROVERSY
- 3. DISCUSS EVIDENCE FOR AND AGAINST THE SUBCLINICAL NATURE OF SCT
- 4. DESCRIBE POTENTIAL MECHANISMS CONNECTING SCT WITH EXERTIONAL EVENTS
- 5. DISCUSS A RECENT PILOT STUDY

SICKLE CELL DISEASE

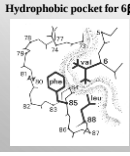
- HEMOGLOBIN S
  - HISTORY
    - FIRST IDENTIFIED IN 1910 IN CHICAGO (DR. JAMES B. HERRICK) ON A BLACK CARIBBEAN DENTAL STUDENT
    - CHARACTERIZED FROM THE 1940S TO THE 1970S
  - DEFINITION
    - A GENETIC MUTATION OF A SINGLE NT IN THE BETA GLOBIN GENE THAT CHANGES 1 CODON THAT RESULTS IN ONE AMINO ACID SUBSTITUTION YIELDING A HEMOGLOBIN THAT POLYMERIZES UNDER LOW OXYGEN TENSIONS CHANGING THE SHAPE OF THE RBCS CAUSING OBSTRUCTION, HYPOXIA, AND HEMOLYSIS.
  - INHERITANCE
    - HOMOZYGOUS (SCD) AND HETEROZYGOUS (SCT)
    - COMPOUND HETEROZYGOTES (HBSC AND HBS/B-THAL)
  - ETIOLOGY
    - THE SUBSTITUTION OF A VALINE (+0) FOR A GLUTAMIC ACID (-1) AT THE 6TH POSITION OF THE BETA CHAIN (CHANGE IN CHARGE OF +1)
      - $(A_2B_2^{6GLU->VAL})$
  - PATHOPHYSIOLOGY
    - LOW O_2 (<85%) > DEOXYHB > POLYMERIZATION > SICKLE CELL FORMATION > VASO-OCCLUSION > ANEMIA

DEOXYHEMOGLOBIN S POLYMER STRUCTURE

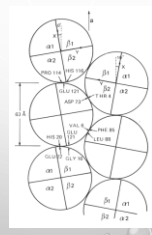
Charge and size prevent 6β Glu from binding.



Hydrophobic pocket for 6β Val

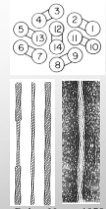


Paired strands of deoxy Hb S (crystal structure)



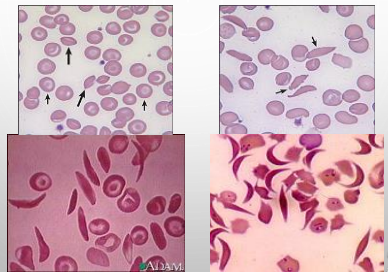
Wishner, JMB 1975

Deoxyhemoglobin S 14-stranded polymer (electron micrograph)



Dykes, Nature 1978; JMB 1979
Crepeau, PNAS 1981

SICKLE CELL DISEASE



HEALTH ISSUES WITH SICKLE CELL TRAIT (1930S-70S)

- MORTALITY
  - 1933: 1ST REPORT OF SCT EXHIBITING SHORTENED LIFESPAN
  - 3 EARLY STUDIES BETWEEN 1940S-1958 SUGGESTED SHORTENED LIFESPAN (FLAWED)
  - 9 SUBSEQUENT STUDIES BETWEEN 1966-1975 SHOWED NO REDUCTION IN LIFESPAN
- HOSPITALIZATIONS
  - 2 STUDIES IN 1952 & 1975 SHOWED NO INCREASE IN HOSPITALIZATION FOR SCT
- GROWTH & DEVELOPMENT
  - 4 STUDIES (1974-1980) SHOWED NO DIFFERENT IN HEIGHT, WEIGHT, OR CLASSROOM ACHIEVEMENT FOR SCT CHILDREN BUT DELAYS IN SKELETAL DEVELOPMENT (1975 X 2)
- MULTIPLE HEALTH ISSUES REPORTED
  - SPLENIC INFARCTS (ALTITUDE OR ANESTHESIA), PREGNANCY, NEWBORNS, INFECTIONS, RENAL DYSFUNCTION, HEMATOLOGIC ABNORMALITIES, NEUROLOGICAL, OPHTHALMOLOGICAL, PULMONARY, BONE, LEG ULCERS

ALTITUDE AND SPLENIC INFARCTS WITH SCT

- BETWEEN 1950-1954: 4 PAPERS REPORTED INFARCTS IN PLANES >10,000 FT
  - HB ELECTROPHORESIS & SPLENECTOMY WAS NOT PERFORMED ON ALL SUBJECTS
- IN 1955: 15 BLACK SOLDIERS SUFFERED SPLENIC INFARCTS IN PLANES >10,000 FT
  - 11 WERE AS, 3 WERE SC, & 1 WAS SICKLE/THAL
- A 1956 STUDY SUGGESTED HBS >40% (LATER >35%) PREDISPOSED TO SPLENIC INFARCTS
- 1956-1971: 6 PAPERS WITH 15 SUBJECTS WITH SPLENIC INFARCTS ON PLANES
- NO REPORTS OF ADVERSE EVENTS IN AS PEOPLE PRESSURIZED PLANE CABINS
  - PRESSURIZED CABINS ARE EQUIVALENT TO 7,500 FEET ALTITUDE
- 1961 & 1972: SPLENIC INFARCTS: DRIVING IN ALPS AND MOUNTAIN CLIMBING
- CONTROLLED ALTITUDE STUDIES USING SCT SUBJECTS WERE CONFLICTING

SURGERY/ANESTHESIA AND SCT

- BETWEEN 1949-1976 >17 REPORTS ASSOCIATED SURGERY/ANESTHESIA & SCT
  - >700 SUBJECTS/PATIENTS WERE INCLUDED IN THESE REPORTS
  - DEATHS AND COMPLICATIONS WERE NOTED TO INCLUDE SPLENIC INFARCTS
  - MANY RESUMED SCT (+ SCREEN) WITHOUT HB ELECTROPHORESIS CONFIRMATION
  - SEVERAL PRESUMED THE CONTRIBUTION OF SCT USING POST-MORTEM SICKLING
  - ONE CONTROLLED STUDY FROM 1974 SHOWED NO DIFFERENCE
    - IT WAS MATCHED FOR AGE, GENDER, SURGICAL PROCEDURE
    - NO DIFFERENCE IN FREQUENCY OR TYPE OF COMPLICATION OR LENGTH OF HOSPITAL STAY
- SEVERAL REPORTED NO ISSUES AS LONG AS OXYGEN WAS MAINTAINED

PREGNANCY/NEWBORN WITH SCT

- BETWEEN 1948-1976: >20 REPORTS DESCRIBING SCT & PREGNANCY/NEWBORNS
- MOST REPORTS FOUND NO DIFFERENCE BETWEEN SCT AND CONTROL
  - PREGNANCY
    - PREMATURE LABOR, C-SECTION, INFECTIONS, HEMORRHAGE, TOXEMIA, MORTALITY
  - NEWBORNS
    - APGAR, HCT, BILIRUBIN, PHYSICAL EXAM, NEURO EXAM, FETAL LOSS, STILL BIRTHS, SPONTANEOUS ABORTIONS
- FEW REPORTS SHOWED DIFFERENCES
  - 1 STUDY REPORTED LOWER BIRTH WEIGHTS WITH SCT

INFECTIONS WITH SCT

- BETWEEN 1944-1976: >21 REPORTS ASSOCIATING SCT & INFECTIONS
  - SEVERAL REPORTS DOCUMENTED PROTECTION AGAINST MALARIA WITH SCT
    - HBS CONTAINING RBCS SICKLE EASIER AND ARE CLEARED FASTER (FALCIPARUM)
    - DUFFY-NEGATIVE RBCS ARE RESISTANT TO MALARIA INFECTIONS (KNOWLESI & VIVAX)
  - CONFLICTING REPORTS FOR SEVERAL TYPES OF BACTERIAL INFECTIONS
    - PNEUMONIA, TB, ABSCESSES, ENTERITIS, LEPROSY, UTI
    - PYELONEPHRITIS AND UTI ARE LIKELY TO BE HIGHER IN SCT

RENAL & GENITOURINARY ABNORMALITIES

- BETWEEN 1948-1977: >25 REPORTS (>250 SUBJECTS) DESCRIBE HEMATURIA
  - SOME STUDIES REPORT HIGHER PREVALENCE OF HEMATURIA IN SCT VS CONTROLS
  - ONCE HEMATURIA OCCURS, IT IS LIKELY TO RECUR IN SCT
  - MANY PATIENTS WITH SCT ALSO HAD CONCOMITANT HEMATURIA CAUSING CONDITIONS
- BETWEEN 1963-1976: >8 REPORTS OF HYPOSTENURIA & >5 PAPILLARY NECROSIS
- CONTROLLED STUDIES SHOWED NO DIFFERENCE IN CREATININE/INULIN CLEARANCE
- NORMAL RENAL PATHOLOGY BUT MORE GLOMERULAR AREA/CORTICAL AREA
- SINGLE CASE REPORTS: CHRONIC RENAL FAILURE, THROMBOSIS/INFARCTION, NEPHROTIC SYNDROME
- SHORT-TERM SURVIVAL FOLLOWING RENAL TRANSPLANT IS SIMILAR IN SCT (1980)
- BETWEEN 1961-1970: >5 CASES REPORTS OF PRIAPISM

HEMATOLOGIC ISSUES WITH SCT

- NO DIFFERENCES IN HCT WERE REPORTED BETWEEN SCT & CONTROLS
  - SCT SICKLE CELLS AT REST ARE ABOUT 0.05% AND RAISES TO 1-25% DURING EXERCISE
- SCT RBCS SHOWED NORMAL SURVIVAL BUT INCREASED SPLENIC SEQUESTRATION
- RHEOLOGICALLY, OXYGENATED RBCS HAD SIMILAR VISCOSITY AS CONTROLS
  - DEOXYGENATED RBCS FROM SCT WERE SIGNIFICANTLY MORE VISCOUS
- SCT BLOOD SHOWED 1% SICKLING STORED IN ACD FOR 28 DAYS
  - NO ISSUES WITH RECIPIENTS WHEN TRANSFUSED SCT BLOOD
- SCT BLOOD FROZEN UNDERWENT EXCESSIVE HEMOLYSIS UPON THAWING
- ONE REPORT SHOWED A REACTIVITY OF SCT RBCS TO ANTI-I AND ANTI-LITTLE I
- ONE REPORT SHOWED SLIGHTLY HIGHER HBF IN SCT THAN CONTROLS

OTHER ISSUES ASSOCIATED WITH SCT

- NEUROLOGICAL ABNORMALITIES
  - A VARIETY OF NEUROLOGICAL ABNORMALITIES WERE REPORTED: SOME DUE TO THROMBOSIS
  - NO DIFFERENCE IN CEREBROVASCULAR ACCIDENTS BETWEEN SCT AND CONTROLS
  - 1 STUDY SHOWED 60% COMPLICATED MIGRAINES WITH SCT VS 20% COMPLICATED W/O SCT
- OPHTHALMOLOGICAL ABNORMALITIES
  - MANY SINGLE CASE REPORTS WERE PUBLISHED FROM 1954-1979 SHOWING EYE ISSUES
    - HEMORRHAGE, OCCLUSIONS, INFARCTIONS, ISCHEMIA, TRANSIENT MONOCULAR BLINDNESS, PERIPHERAL RETINAL VASCULAR PROLIFERATION, TORTUOSITY OF RETINAL VESSELS, MICROANEURYSMS, SHEATHING OF RETINAL VESSELS, PROLIFERATIVE RETINOPATHY, DETACHED RETINA, OPTIC ATROPHY, GLAUCOMA
  - MORE SICKLING IN THE AQUEOUS HUMOR THAN IN BLOOD OF SCT SUBJECTS (1979)
  - NO INCREASE IN PREVALENCE OR SEVERITY OF DIABETIC RETINOPATHY WITH SCT (1979)
  - DELAY IN HYPHEMA RESOLUTION AND POTENTIAL CONNECTION TO GLAUCOMA (1979-1985)

OTHER ISSUES ASSOCIATED WITH SCT

- PULMONARY & CARDIOVASCULAR ABNORMALITIES
  - PULMONARY EMBOLISMS IN PATIENTS WITH SCT (2.2%) VS CONTROL (1.5%) ($P < 0.001$)(RR=1.5)
    - NO DIFFERENCE IN RECOVERY, DEATH, AND MORBIDITY
  - SINGLE CASE REPORTS OF CARDIOMYOPATHY & MI BUT NO CONTROLLED STUDIES
  - CONTROLLED STUDIES SHOWED NO STATISTICAL DIFFERENT BETWEEN SCT & CONTROLS FOR:
    - BP, HEART SIZE, ECG FINDINGS
- BONE & JOINT ABNORMALITIES
  - 12 CASE REPORTS DESCRIBED AVASCULAR NECROSIS OF THE FEMORAL HEAD
  - CONTROLLED STUDY SHOWED NO DIFFERENCE FOR JOINT SYMPTOMS OR DISEASES
- LEG ULCERS
  - SEVERAL CASE REPORTS OF AS PATIENTS WITH LEG ULCERS
  - CONTROLLED STUDIES SHOWED NO DIFFERENCE OR STATISTICALLY INSIGNIFICANT DIFFERENCES

HEALTH RISKS FOR SCT MID-1970S TO MID-1980S

- NO ASSOCIATION BETWEEN SCT AND:
  - SURVIVAL, MORTALITY, MORBIDITY, HOSPITALIZATIONS, RENAL TX, G6PD INHERITANCE
- CONFLICTING PEDIATRIC DATA: GROWTH, DEVELOPMENT, SCHOOL PERFORMANCE
- SIGNIFICANT ASSOCIATION ALTHOUGH LOW FREQUENCY BETWEEN SCT AND:
  - SPLENIC INFARCTION AT HIGH ALTITUDES (>10,000 FT)
  - UNPRESSURIZED AIR TRAVEL
  - MOUNTAIN CLIMBING
  - BACTERURIA AND PYELONEPHRITIS IN PREGNANCY
  - HYPOSTENURIA/ISOTHENURIA, HEMATURIA
  - DELAYED RESOLUTION OF ANTERIOR CHAMBER HYPHEMA
- ASSOCIATION WITH EXERCISE-RELATED EVENT/DEATH
  - MILITARY AND ATHLETES

ADVERSE EVENTS/DEATHS IN SCT (MILITARY)

- IN 1970: 4 SOLDIERS WITH SCT DIED IN BASIC TRAINING AMONG 4,000 BLACKS
  - 3 COLLAPSED ON DAY 1 OF BASIC TRAINING AND DIED IN 24 HOURS
    - 73 OTHER RECRUITS WITH SCT HAD NO ADVERSE EVENTS TRAINING ALONGSIDE THE 4 WHO DIED
  - IN 1974 (1) & 1977 (4) SOLDIERS WITH SCT HAD ADVERSE EVENTS AND 2 DIED
    - ALL SHOWED RHABDOMYOLYSIS, MYOGLOBINURIA, ACUTE TUBULAR NECROSIS, & DIC
    - NOT SURE HOW MANY SCT RECRUITS DID NOT HAVE EVENTS
  - MILITARY DATA (1977-82), EXERCISE-RELATED DEATH WAS 30X ↑↑ WITH SCT
    - DEATH FROM HEAT STROKE > RHABDOMYOLYSIS, CARDIAC ARRYTHMIAS, ACUTE RENAL FAILURE
  - MILITARY DATA (1982-1986), EXERCISE-RELATED DEATH WAS 21X ↑↑ WITH SCT
    - AGE RELATED: 8X ↑↑ RISK BETWEEN 25-30YO COMPARED TO 18YO (NO ↑↑ RISK IN CONTROLS)
    - HB S RELATED: ↑↑ RISK >35% HBS (40%)
    - RISK NORMALIZES IN SOLDIERS FOLLOWING BASIC TRAINING FOR THE REST OF THEIR CAREER
  - 39 TOTAL EVENTS IN THE MILITARY BETWEEN 1967-1994 IN SOLDIERS WITH SCT
  - RUN 1-3 MILES; 11-14 X BASAL METABOLIC RATE FOR 5-30 MINUTE, UNTRAINED

ADVERSE EVENTS/DEATHS IN SCT (ATHLETES)

- BETWEEN 1957-1963: 7 SCT CIVILIANS DIED SUDDENLY
  - STUDY IN 1961 SHOWED NO DIFFERENCE IN BLACK DEATHS BETWEEN SCT & NO SCT
- EXERCISE-RELATED DEATHS OR EVENTS OCCUR LESS OFTEN IN ATHLETES THAN SOLDIERS
- IN 1973 A SURVEY STUDY REPORTED THAT 6.7% OF NFL PLAYERS HAS SCT
  - US PREVALENCE OF SCT AT THE TIME WAS 7.7% & TEAM PHYSICIANS NOTED NO PROBLEMS
- NO ISSUES WITH BLACK ATHLETES AT THE 1968 OLYMPICS IN MEXICO CITY
  - ALTITUDE OF 7,000 FEET & SCT WAS DOCUMENTED IN 2 DISTANCE RUNNERS
- IN 1974 A COLLEGE FOOTBALL PLAYER DIED DURING THE FIRST DAY OF PRACTICE
  - HIGH ALTITUDE, ACUTE RENAL FAILURE, NO RHABDOMYOLYSIS
- A 1976 STUDY ON 5 SCT NON-ATHLETES - BICYCLED TO NEAR MAX HEART RATE
  - NO SICKLE CELLS AT REST BUT SOME FOLLOWING EXERCISE & NONE IN CONTROL GROUP & NO ADVERSE EVENTS
- 1974 & 1976 STUDIES SHOWED NO DIFFERENCE IN ENERGY EXPENDITURE OR EXERCISE CAPACITY FOR SCT COMPARED TO CONTROLS
- TOTAL OF 8 CIVILIAN EVENTS BETWEEN 1974-1993 WITH SCT (MOSTLY ATHLETES)
  - DEATHS IN 10 COLLEGE FOOTBALL PLAYERS
- 1996-2008: 16 NON-ATHLETE CIVILIANS HAD ADVERSE EVENTS CONNECTED TO SCT
  - 15X GREATER RISK OF EXERCISE-RELATED DEATH FOR ATHLETES & 37X GREATER RISK IN FOOTBALL

MILITARY AND NCAA RESPONSES

- MILITARY REGULATIONS
  - 1973 POLICY PERTAINED TO ALL BRANCHES EVENLY WITH RESTRICTED DUTIES
  - 1981 RESTRICTIONS WERE LIFTED IF HBS ≤41%
  - 1985 ALL RESTRICTIONS WERE LIFTED AND NO SCREENING WAS REQUIRED
  - 1996 MODIFICATIONS SPECIFIC TO MILITARY BRANCH
    - ARMY CEASED TO SCREEN FOR HBS: REEVALUATED AFTER 8 DEATHS IN 1999/2000
    - MARINES SCREENED BUT MAINTAINED IDENTICAL PROTOCOLS FOR SCT
    - AIR FORCE SCREENED AND OFFERED OPTION TO DECLINE MILITARY SERVICE (HBS>45% MUST LEAVE)
    - NAVY SCREENED AND TAGGED SCT RECRUITS WITH A RED TAG AND BELT (HBS>45% MUST LEAVE)
    - NIH RECOMMENDED THE MILITARY STOP SCREENING FOR HBS AND DEVELOP UNIVERSAL STANDARDS
- NCAA POLICIES
  - 1975 NCAA ISSUED COMMENTS TO ALERT SCT ATHLETES TO RISKS
  - 2010 ALL DIVISION I NCAA ATHLETES MUST PROVIDE PROOF OF SCT STATUS OR SIGN WAIVER
    - 2012 FOR DIVISION II
  - ASH RELEASED A STATEMENT RECOMMENDING THE NCAA TO REVERSE THE POLICY
    - CHANGE TRAINING REGIMENS UNIVERSALLY TO REDUCE ALL EXERCISE RELATED EVENTS

SAFETY PROTOCOLS FOR SCT (OR UNIVERSAL)

- START SLOW
  - PRETRAINING BEFORE HEAVY EXERTION
  - HYDRATION
  - BREAKS (ALLOW RECOVERY TIME)
  - LIGHTER CLOTHS/PACKS/PADS FOR FOOTBALL
  - PERIODS OF COOLING (A/C)
  - DON'T TRAIN ILL OR SHORTLY AFTER RECOVERY (VIRAL)
- ADJUSTMENT PROTOCOLS BASED ON:
  - CONCOMITANT DIAGNOSES (CARDIAC, THROMBOTIC)
  - WEATHER
  - ALTITUDE

EVIDENCE SUPPORTING SCT AS SUBCLINICAL DISEASE

- 1ST SCT REPORT IN 1933 SUGGESTED HIGHER MORTALITY
- DISCUSSION STARTED IN MID-1940S & INCREASED IN THE 1960S-1970S
  - MANY REPORTS OF EXERCISE-RELATED SUDDEN DEATHS AND NON-FATAL ADVERSE EVENTS
    - MOSTLY CASE REPORTS VS CONTROLLED STUDIES
    - EARLY REPORTS PRESUMED SCT STATUS BUT DID NOT CONFIRM BY HB ELECTROPHORESIS
    - FALSE PRESUMPTION OF CAUSE BASED ON POST-MORTEM INTRAVASCULAR SICKLING
  - MANY REPORTS ABOUT HEALTH ISSUES
    - 1950-1970: SPLENIC INFARCTS WITH HIGH ALTITUDE AND SURGERY
    - 1944-1976: INCREASED INFECTIONS PARTICULARLY PYELONEPHRITIS AND UTI ARE LIKELY TO BE HIGHER IN SCT
    - 1948-1977: >25 REPORTS (>250 SUBJECTS) DESCRIBE HEMATURIA AND RENAL DISEASE
    - 1954-1979: MANY SINGLE CASE REPORTS SHOWING EYE ISSUES
      - HEMORRHAGE, OCCLUSIONS, INFARCTIONS, ISCHEMIA, TRANSIENT MONOCULAR BLINDNESS, PERIPHERAL RETINAL VASCULAR PROLIFERATION, TORTUOSITY OF RETINAL VESSELS, MICROANEURYSMS, SHEATHING OF RETINAL VESSELS, PROLIFERATIVE RETINOPATHY, DETACHED RETINA, OPTIC ATROPHY, GLAUCOMA
- MID-1970S TO MID-1980S PRODUCED CONTROLLED STUDIES & CONTROVERSIAL RESULTS
- 2005: AJAYI ASKS THE QUESTION IF SCT SHOULD BE RECLASSIFIED AS A DISEASE STATE
- 2007: MITCHEL CHALLENGES MEDICINE TO SCREEN AND ADJUST TRAINING ACCORDINGLY

OTHER SIDE OF THE DEBATE

- EXERCISE-RELATED EVENTS ALSO HAPPEN IN NON-SCT
- SCT ATHLETES AND WARFIGHTERS HAVE BEEN SUCCESSFUL
  - MANY ATHLETES AND WARFIGHTERS WITH SCT ARE EVENT-FREE
  - % WITH SCT RUNNING THE ABIDJAN SEMI-MARATHON IS SAME AS POPULATION (IVORY COAST)
  - SAME FOR MT. CAMEROON ASCENT RACE (WC AFRICA)
  - SOME US OLYMPIC SPRINTERS HAVE BEEN SCT
  - MORE IVORY COAST TRACK & FIELD CHAMPIONS WITH SCT THAN IN POPULATION
    - WOMEN'S HIGH JUMP (90.9% SCT) AND MEN'S SHOT PUT (87.5% SCT)
    - 32/33 RECORDS FOR SPRINT RACES HAD SCT
    - SCT HAVE BETTER PERFORMANCE DURING JUMP AND REACH TESTS
    - SCT HAVE HIGHER TYPE IIX MUSCLE FIBERS (BRIEF/EXPLOSIVE MOVEMENTS)
  - NO DIRECT EVIDENCE THAT DEATH IS CAUSED BY SICKLE CELL OBSTRUCTION
    - THESE DEATHS DO NOT INVOLVE INFARCTION OF SPLEEN, KIDNEYS, LUNG, BONE, RETINA, BRAIN
  - FEW REPORTS IN SCD OF EXERTIONAL MORTALITY, MI, ANGINA, RHABDOMYOLYSIS
    - SCD GROUP RARELY EXERTS, AVOIDS THE MILITARY, ATHLETICS, AND ALTITUDES
    - REPORTS OF REDUCED ATHEROSCLEROSIS IN SCD

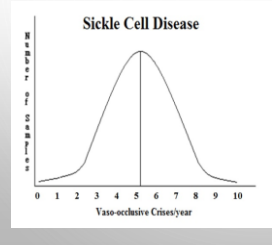
MECHANISMS AND BIOMARKERS DURING SCT EVENTS

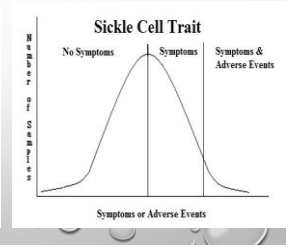
- RHABDOMYOLYSIS
  - SCT ARE 100-200X RISK OF DEVELOPING EXERTIONAL RHABDOMYOLYSIS
    - EXERTIONAL HEAT ILLNESS > RHABDOMYOLYSIS, THROMBOSIS, RENAL FAILURE, CARDIAC ARRHYTHMIAS > ADVERSE EVENT > DEATH
    - HEAT ILLNESS: CORE TEMP, ABG (ACIDOSIS), ↓↓ GLUCOSE, ↑↑ LACTATE
    - RHABDOMYOLYSIS: ↑↑ CK, ALT, AST, LD, URINE MYOGLOBIN, URINALYSIS (↑SP. GR. BLOOD)
- ACTIVATION OF THE COAGULATION SYSTEM
  - (2007) SCT HAVE 2X INCREASED RISK OF VTE, 4X INCREASED RISK FOR PE, 7% OF SCT HAVE VTES
  - INCREASED VWF, D-DIMER, TFIII, FIBRINOPEPTIDE, PROTHROMBIN F1.2, THROMBIN/ANTITHROMBIN COMPLEX, DECREASED ATIII/PROTEIN C/S, ABNORMAL PFA-100
    - MAY EXPLAIN SPLENIC INFARCTS, HEMATURIA, ISOTHENURIA, & EXERCISE-RELATED ADVERSE EVENTS
  - SOME SCT PATIENTS DEVELOPED DIC
- RENAL DISEASE (RENAL INFARCTS OR MYOGLOBINEMIA)
  - ELECTROLYTES (ANION GAP >30 & HYPERKALEMIA), ↑↑ BUN, CREATININE, URIC ACID,

SCT AND EXERCISE

- CAN EXERTIONAL EVENTS BE INITIATED AND MEASURED IN CONTROLLED STUDIES?
- CONTROLLED STUDIES SHOWED NO DIFFERENCE AFTER EXERCISE FOR SCT & AA
  - NORMAL ECG, LUNG/HEART FUNCTION, GAS TRANSPORT, O_2 CONSUMPTION, METABOLIC RECOVERY, "GETTING INTO SHAPE"
  - SICKLE CELL NUMBERS ↑↑ AFTER EXERCISE (1%) AND MORE WITH HIGHER ALTITUDES
    - 18,000 FT (2-5%), LUNG SCANS SHOWED MICROVASCULAR INFARCTS IN 50% BUT NORMAL LUNG FUNCTION
    - MAY BE CONNECTED TO SPLENIC INFARCTS AND RENAL PAPILLARY INFARCTS
  - DIFFICULT TO SHOW MORTALITY RELATIONSHIP BECAUSE DEATHS OCCUR INFREQUENTLY
  - UNETHICAL TO INDUCE EVENTS IN RESEARCH SUBJECTS
  - RISKY TO INCLUDE HEAVY EXERTION INTO RESEARCH PROTOCOLS
  - BLOOD BIOMARKERS WERE NOT MEASURED

HYPOTHESIS TO EXPLAIN VARIABILITY





PILOT STUDY FOR ABNORMAL BIOMARKERS IN SCT AT REST

- 4 AS SUBJECTS AND 4 AA CONTROL SUBJECTS
- COLLECTED BLOOD & URINE 4 TIMES FOR EACH SUBJECT SEVERAL WEEKS APART
- ALL SUBJECT'S GENOTYPES WERE CONFIRMED
- MEASURED 2 BIOMARKERS FOR HYPERCOAGULABILITY
  - D-DIMER & FIBRIN MONOMER
- MEASURED 4 BIOMARKERS FOR MUSCLE DAMAGE
  - CK, HAPTOGLOBIN, TP, U/A (BLOOD)
- MEASURED 3 BIOMARKERS FOR RENAL DYSFUNCTION
  - U/A (SP.GR., PROTEIN), MICROALBUMIN
- STUDY FUNDED BY ASCLS E & R GRANT

PILOT STUDY FOR ABNORMAL BIOMARKERS IN SCT AT REST

- RESULTS
  - ALL RESULTS WERE NORMAL IN ALL AA SAMPLES (4 SUBJECTS; 16 SAMPLES)
  - HYPERCOAGULABILITY IN SCT
    - D-DIMER WAS ELEVATED IN 3/4 SUBJECTS AND 9/16 SAMPLES (56.25%)
    - FIBRIN MONOMER WAS ELEVATED IN 2/4 SUBJECTS AND 2/16 SAMPLES (12.5%)
  - MUSCLE DAMAGE
    - CK WAS ELEVATED IN ONE SCT SUBJECT (1/4) & ONE SAMPLE (1/16)
    - MEAN CK AND TP WERE HIGHER IN SCT THAN IN CONTROL BUT NOT STATISTICALLY SIGNIFICANT
    - MEAN HAPTOGLOBIN WAS LOWER IN SCT THAN IN CONTROL BUT NOT STATISTICALLY SIGNIFICANT
  - RENAL DYSFUNCTION
    - NO DIFFERENCES IN URINALYSIS AND MICROALBUMIN RESULTS

PILOT STUDY FOR ABNORMAL BIOMARKERS IN SCT AT REST

- CONCLUSIONS
  - HYPERCOAGULABILITY AT REST
    - ALL SCT SUBJECTS DEMONSTRATED EVIDENCE OF HYPERCOAGULABILITY
      - 2 SCT SUBJECTS DEMONSTRATED ELEVATED D-DIMER BUT NOT FIBRIN MONOMER
      - 1 SCT SUBJECT HAD ELEVATED FIBRIN MONOMER BUT NOT D-DIMER
      - 1 SUBJECT SHOWED ELEVATION OF BOTH D-DIMER AND FIBRIN MONOMER
    - SCT SUBJECTS WERE ELEVATED ONE DAY AND NOT THE NEXT
      - 1 SCT SUBJECT WAS ELEVATED FOR D-DIMER ALL FOUR COLLECTIONS
  - MUSCLE DAMAGE
    - CK AND TP WERE HIGHER IN SCT AND HAPTOGLOBIN WAS LOWER (NOT STATISTICALLY SIGNIFICANT)
- QUESTIONS
  - DO ELEVATIONS AT REST SUGGEST CHRONIC ACTIVATION INDEPENDENT OF EXERTION?
  - CAN ELEVATIONS AT REST PREDICT RISK OF EXERTIONAL EVENTS?
  - WILL ALL VALUES ELEVATED AT REST INCREASE WITH EXERTION?
  - IF ELEVATED AT REST, WILL THE LEVEL INCREASE MORE DRAMATICALLY WITH EXERCISE?

FUTURE STUDIES

- STUDY DESIGN
  - INCREASE THE STUDY N (30-50 SUBJECTS IN EACH GROUP)
  - USE AGE, RACE, AND GENDER MATCHED CONTROL GROUP
  - MEASURE MORE BIOMARKERS FOR HYPERCOAGULABILITY, MUSCLE DAMAGE, AND RENAL DYSFUNCTION
  - MEASURE THEM AT REST AND FOLLOWING TREADMILL EXERTION
  - MEASURE EACH SUBJECT SERIALLY, SEVERAL WEEKS APART (AT LEAST 4 TIMES)
- QUESTIONS
  - WILL PATTERN CONTINUE WITH SOME SCT BEING POSITIVE AND SOME NEGATIVE AT REST?
  - WILL EXERTION ELEVATE THESE VALUES IN ALL SUBJECTS?
  - WILL ELEVATIONS BE MORE DRAMATIC IN THOSE WITH RESTING ELEVATIONS?
  - CAN RESTING ELEVATIONS PREDICT EXERTIONAL ELEVATIONS?

IS SICKLE CELL TRAIT A BENIGN CARRIER?
OR
IS SICKLE CELL TRAIT A CLINICAL CONDITION?

WHAT IS YOUR OPINION?????

THANK YOU!!!

QUESTIONS???