NWU®

Inaugural Lecture

by

PROF EMMANUEL MUKWEVHO

Topic:

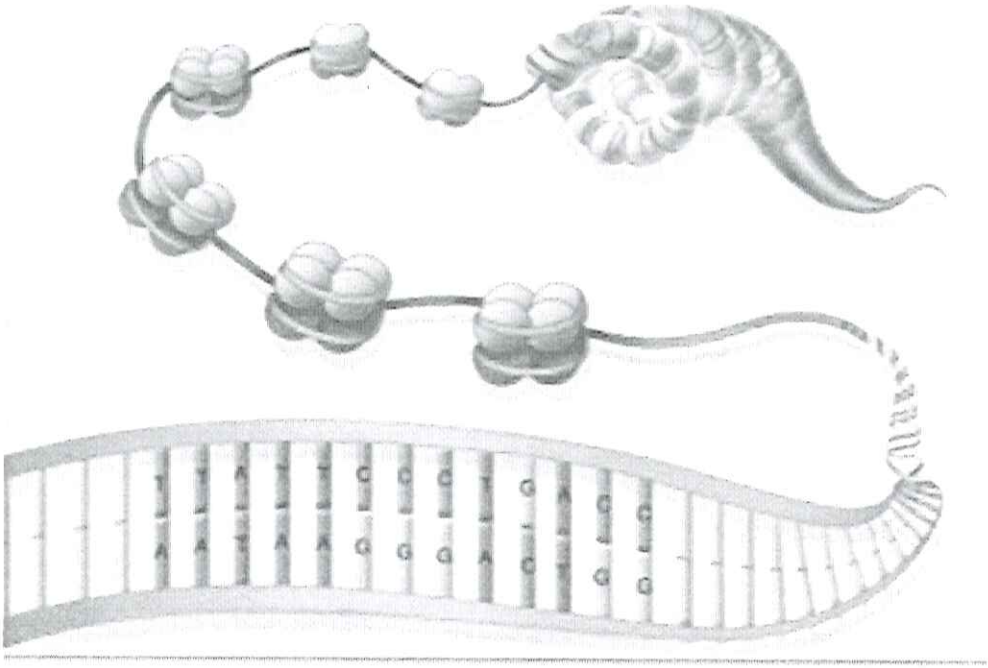
Chromatin Remodeling: The Epigenetics of NRF-I in Diabetes & Obesity Therapeutics

Date:
Wednesday, 15 August 2018

Time: 18h00 for 18h15

Venue:
North-West University, Mafikeng,
Lecture Room A1-G45

FACULTY OF NATURAL AND AGRICULTURAL SCIENCES



PROFILE:

Academic Profile:

Prof Mukwevho holds BSc (Univen), BSc Hons (UL) MSc (UCT), PhD (UCT) and Certificate in Financial Management (UCT) and Certificate in Project Management (UCT). He is currently in a process of submitting his MBA thesis having already completed all its course work at NWU. He graduated for his PhD in June 2010 and employed as Lecturer that very year at the University of Johannesburg (Kingsway Campus) in the department of Biochemistry. He was then promoted to Senior Lecturer at University of Johannesburg in November 2012, where he also served in the Science Faculty board for 5 years and also a Biochemistry Academic Advisor committee member to the Food Technology at UJ. He was then head hunted to NWU in 2014 as an Associate Professor and joined NWU, 1st October 2014. He was promoted to a Full Professor of Biochemistry in 1st January 2017. He has also received an NRF rating of Y2 in 1st January 2017 (Rating recognition given to young scientist under the age of 40). He also serves as a Subject Chair of Biochemistry in Mafikeng since 2016. He has been involved in various activities with the department of Science & Technology of SA.

Research Focus:

His research focus in on Obesity, Diabetes and Metabolic Syndrome where he focuses on Molecular pathways and signaling molecules involved. In this regard he studies these events within the cell by the use of Mice, Rats, Human Beings and Cell cultures models from the chromatin to the protein level. Both Lipids and Carbohydrate metabolism are the focus, as they are the major events in the etiology and pathogenesis of the metabolic disorder. Furthermore, he studies these pathways with the view of finding novel therapeutics to manage and cure Diabetes, Obesity and Metabolic Syndrome. Exercise, plants extracts and synthesized compounds such TZDs are explored in the quest of finding a cure and better management of these disorders. In the three years Prof Mukwevho has been in NWU, has produced postgraduate students at all levels.

In Research funding, Prof Mukwevho has been funded under Thuthuka for 6 years by National Research Foundation, and now as a rated researcher funded through the 'Incentive for Rated Researchers' and the 'Competitive Incentive for Rated Researchers'.

Postgraduate students Production:

Since joining NWU, 3 years ago, he has produced already 7 MSc students (Molepo, Masilo, Matumba, Isaiah, Munansangu, Masinye & Faskiu) and 3 PhDs (2 in NWU- [Dr Ayeleso Betty & Dr John Owonobi] & one PhD produced at WITS (Nyakunda) through the existing collaboration with Prof Kennedy Erlwenger. He has also trained 4 Post-Docs (Dr Ayeleso, Dr Fuku, Dr Amal & Dr Tella since joining North West University 3 years ago, two of which are in tenure positions and are Senior Lecturers, one in SA and another in Nigeria.

He has also produced about 15 BSc Hons graduates also all from North West University only.

Involvement in Committees worldwide & Collaborations:

He serves in many International journals and reviewed for groups such Elsevier, Wiley, and Springer. In research funding, he has reviewed national for the National Research Foundation (NRF) and internationally, the American Heart Association (AHA). Collaborations that exist with Prof Mukwevho are with Melbourne University (Prof Mark Hargreaves -DVC Research & Postgraduate) in Australia, Cambridge University-(Prof Nick Gay) in the UK, Texas Southern University with Prof Mozayani, Ashraf in USA and many more. Nationally, he collaborate with UCT, Wits, UJ, UKZN and CSIR. He has received several funding instruments from the National research Foundation and MRC.

He has just been appointed to serve in the Council of South African Society for Biochemistry & Molecular Biology (SASBMB) which serves to promote the field of Biochemistry & Molecular Biology in the country from 2018-2021. He has also been appointed at CSIR to serve at the institution External Ethics committee from 2018-2021. He is a

member of ASBMB (American Society of Biochemistry & Molecular Biology) and also APS (American Physiological Society). He has been serving also at CHE (Council for Higher Education) since 2012 as a reviewer for the entity for Quality control.

TEACHING & LEARNING

Prof Mukwevho has taught Biochemistry both at undergraduate and Postgraduate Levels both University of Johannesburg and NWU. At UCT he has served as guest Lecturer for Physiology and also in teaching MBCHB 2nd & 3rd students between 2003-2006 under the department of Human Biology. He teaches mostly Introduction to Biochemistry, Metabolism, Research and also Analytical Biochemistry. Passionate in delivering quality in Teaching & Learning.

COMMUNITY SERVICE

Prof Mukwevho has been involved in various projects that imparts communities within South Africa, having served as guest on SABC2, DSTV as Science & Technology experts. In Radio he has also provided many talks as guest experts on issues involving Science and Technology and Lifestyle diseases awareness on SABC Radios. He has been also involved around Mafikeng in Lifestyles Disease awareness campaign.

Chromatin Remodeling:

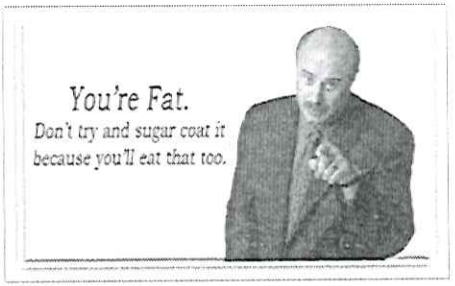
The Epigenetics of NRF-1 in Diabetes & Obesity Therapeutics

PROF E. MUKWEVHO

INAUGURAL LECTURE

Chromatin Remodeling:

The Epigenetics of NRF-1 in Diabetes & Obesity Therapeutics



CONTENT OUTLINE

- **THE PROBLEM**
- ✓ Diabetes- Carbohydrates
- ✓Obesity- Lipids
- ✓Metabolic Syndrome
- **INTERVENTIONS**
- ✓Exercise
- ✓Phytotherapies/Drugs
- ✓Solving the Problem
- Models: Human, Rats & Cell Culture
- ✓NRF-1 ...Link for parallel pathways for Lipids & Glucose
- ✓CaMKII in Lipid and Glucose metabolism
- ✓Output

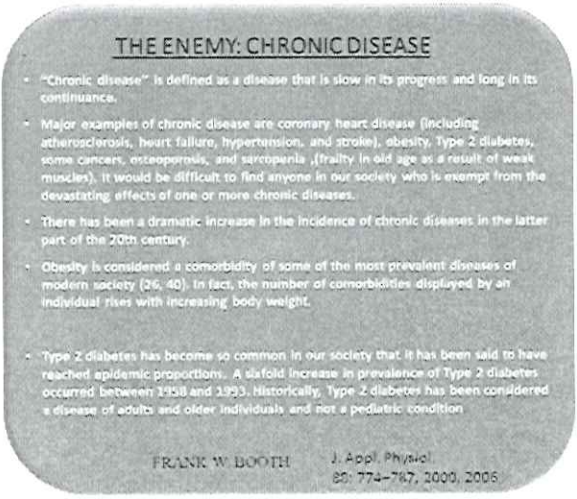
TERMINOLOGIES

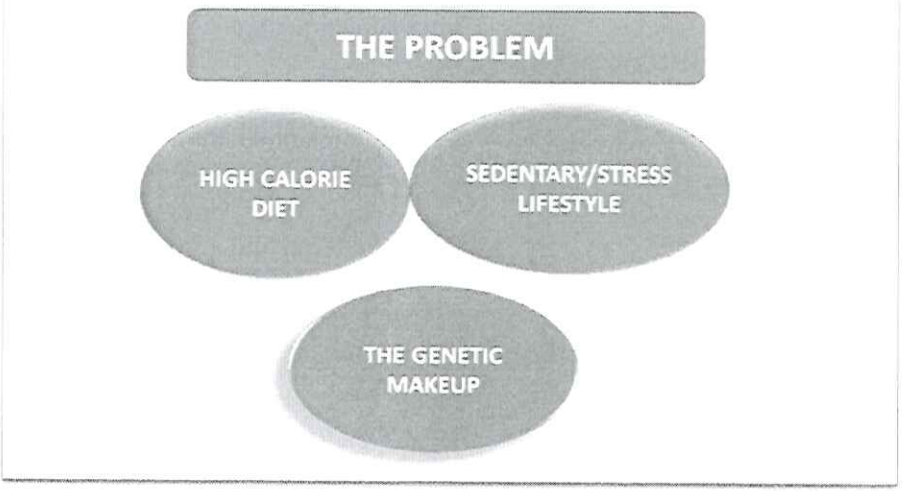
1) DIABETES - is a disease that affects your body's ability to produce or use insulin. Insulin is a hormone. When your body turns the food you eat into energy (also called sugar or glucose).
2) OBESITY - is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health. People are generally considered obese when their body mass index (BMI), a measurement obtained by dividing a person's weight by the square of the person's height, is over 30 kg/m^2, with the range 25–30 kg/m^2 defined as overweight.
3) EPIGENETICS - the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself.
4) THERAPEUTICS-the branch of medicine concerned with the treatment of disease and the action of remedial agents
5) CHROMATIN REMODELING-Chromatin remodeling is the dynamic modification of chromatin architecture to allow access of condensed genomic DNA to the regulatory transcription machinery proteins, and thereby control gene expression.
6) INSULIN RESISTANCE- Insulin resistance (IR) is a condition in which the body's cells become resistant to the effects of insulin
7) NRF-1- its a protein that homodimerizes and functions as a transcription factor which activates the expression of some key metabolic genes regulating cellular growth and nuclear genes required for respiration, heme biosynthesis, and mitochondrial DNA

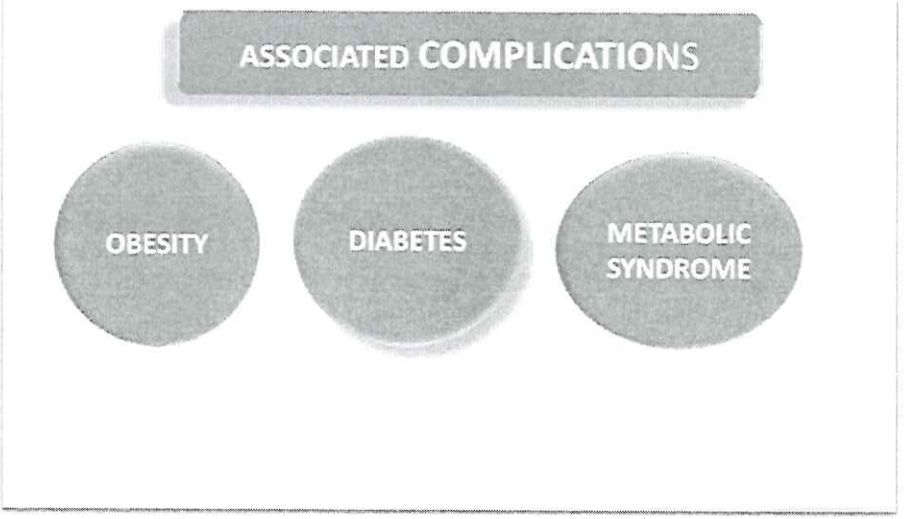
THE COMPLEX, ever busy WORLD

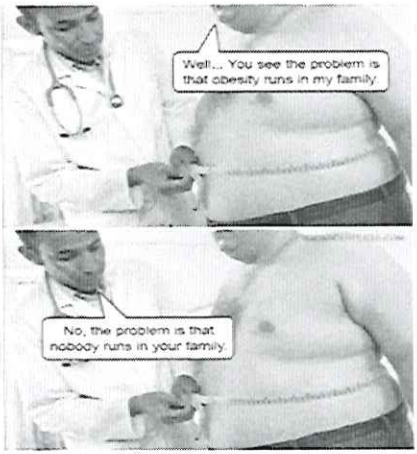
- In the ever changing, fast & busy world, Man has forgotten to Live
- Preoccupied by Unending daily Activities & Deadlines, All these fatigue us
- They put tremendous pressure on the body and alters Normal Cellular events, Hormones and Genes that confers protection against various ailments
- *Even in the Bible God instructed man to rest and do no work at the of the Week*
- The Cell normal Metabolism (Homeostasis) is destabilized consistently and daily because we never rest and always busy.
- Daily **Habitual Activities/Lifestyle** has significant effect on the CELL (the Basic unit of life)
- Once the Cellular activities are altered, Diseases find a way to us, some Fatal
- My Research is understanding Molecular & Cellular events of Cell
- Most Importantly Lifestyle activities: Impact of Exercise, Glucose and Lipid Metabolism in the Cell, especially the **Chromatin**

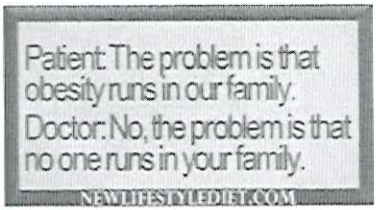
WAGING THE WAR AGAINST OBESITY & DIABETES




THE PROBLEM
HIGH CALORIE DIET
SEDENTARY/STRESS LIFESTYLE
THE GENETIC MAKEUP


ASSOCIATED COMPLICATIONS
OBESITY
DIABETES
METABOLIC SYNDROME





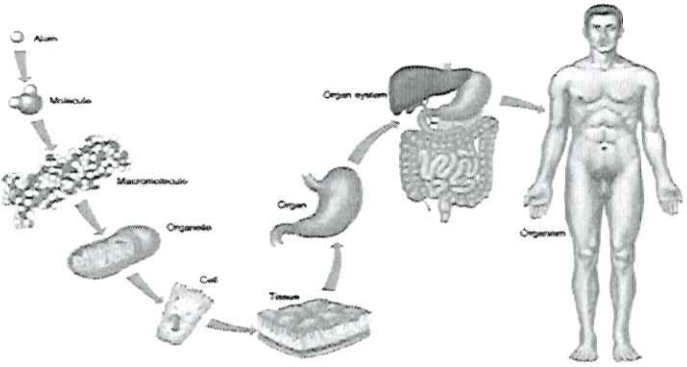
SOCRATES & SHAKESPEAR

- Greek Physician Hippocrates wrote" That which is not used develops and that which is not used waste away.

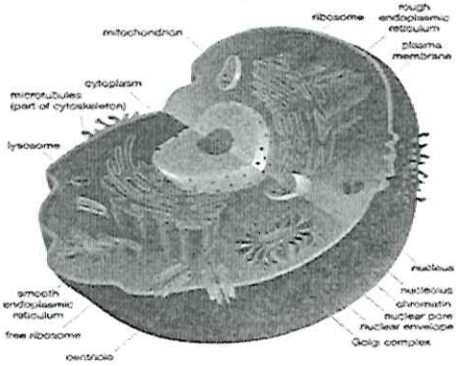
❑ The relevance of this is in Muscle tissue

- Shakespeare writing and plays none of then where death was through Diabetes/Obesity or chronic diseases.

From the Atom to an Organism

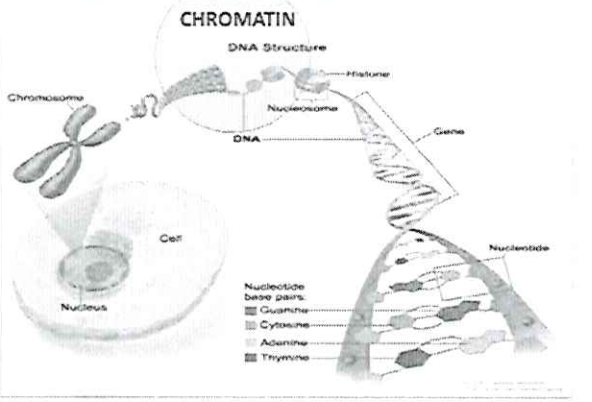


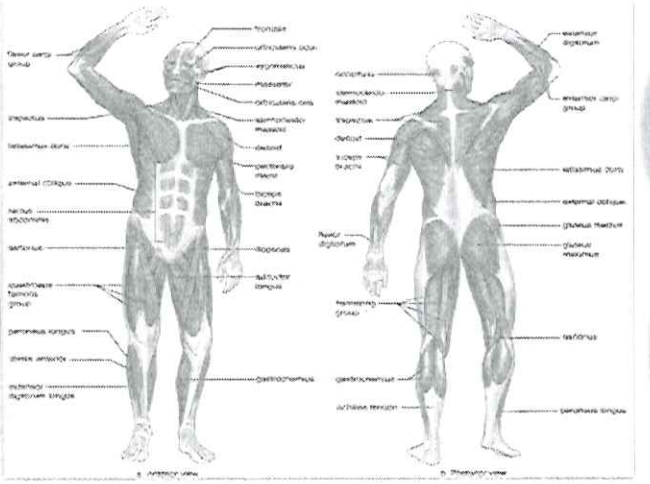
Cell Organelles



- Biochemical Pathways
- Molecular Pathways
- Cellular Pathways

WHATS IT CHROMATIN?





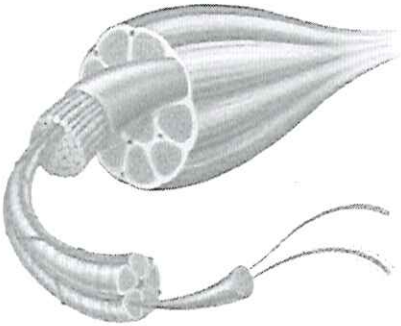
The BODY a Dynamic/ Versatile Instrument

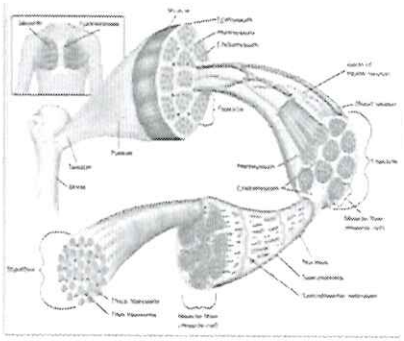
EXPRESSES GENES THAT PROTECTS US FROM DISEASES. THE ADIPOSE TISSUE CELL POSSESSES VARIOUS MOLECULES CRITICAL FOR OUR SURVIVAL

MUSCLE

DYNAMIC TISSUE

Expresses genes that protects us against chronic diseases

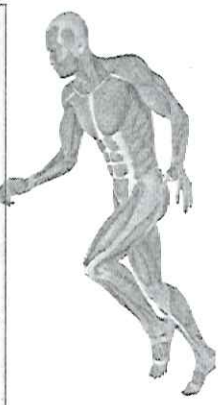




SKELETAL MUSCLE

Skeletal muscle *is an … in their metabolic and contractile properties, including oxidative slow-twitch (type I), mixed oxidative-glycolytic fast-twitch (type IIa) and glycolytic fast-twitch (type IIb) myofibers.*

- ***Type I fibers*** *preferentially express enzymes that oxidize fatty acids, contain slow isoforms of contractile proteins, and are more resistant to fatigue than are glycolytic fibers.*
- ***Type II fibers*** *preferentially metabolize glucose and express the fast isoforms of contractile proteins.*
- *Endurance exercise training triggers a remodeling program in skeletal muscle that progressively enhances performance in athletes such as marathon runners, mountain climbers, and cyclists.*
- *This involves change in metabolic programs and structural proteins within the myofiber that alter the energy substrate utilization and contractile properties that act to reduce muscle fatigue (Fluck and Hoppeler, 2003).*
- *Training-based adaptations in the muscle are linked to increases in the expression of genes involved in the slow-twitch contractile apparatus, mitochondrial respiration, and fatty acid oxidation (Holloszy and Coyle, 1984).*
- *These adaptations that improve performance can also protect against* ***obesity*** *and related* ***metabolic disorders*** *(Koves et al., 2005).*
- *Moreover, skeletal muscles rich in oxidative* ***slow-twitch fibers*** *are resistant to muscle wasting (Minnaard et al., 2005).*



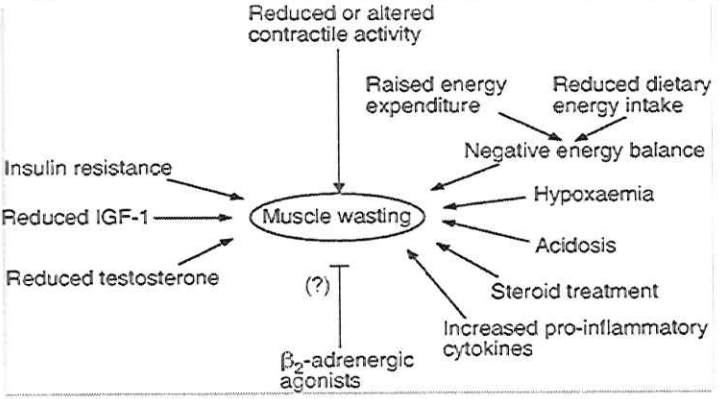
THRIFTY GENES HYPOTHESIS

James Neel's Hypothesis 1962 geneticist

Thrifty genes are genes which enable individuals to efficiently collect and process food to deposit fat during periods of food abundance in order to provide for periods of food shortage (feast and famine).

Hypothesis to explain rising epidemics of metabolic syndrome - obesity and its closely associated co-morbidities.

MUSCLE INACTIVITY (ATROPHY)

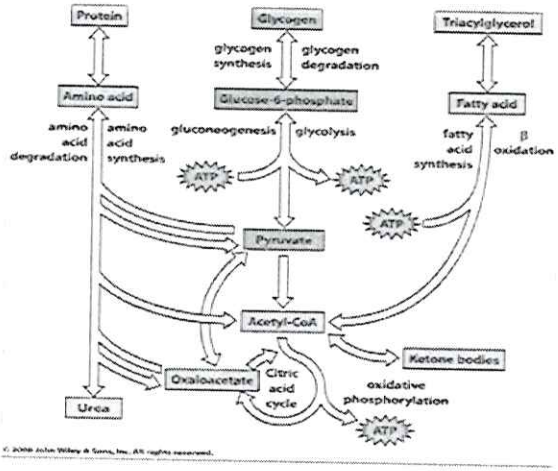


ENERGY SOURCES/FUEL for the BODY

~48h
Glucose (CHO)

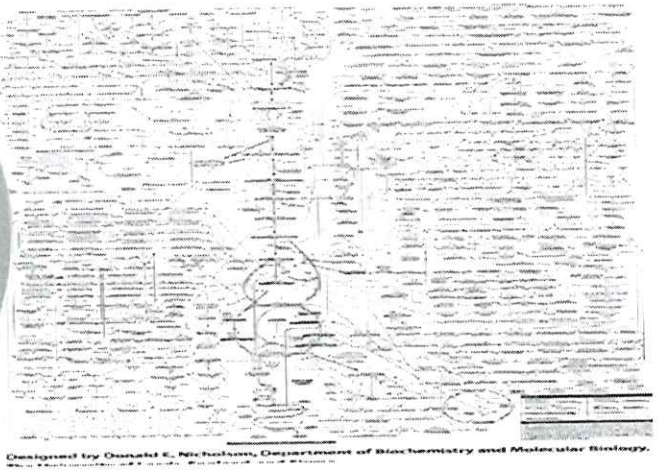
~2-3 Months
Fatty Acids (TGs)

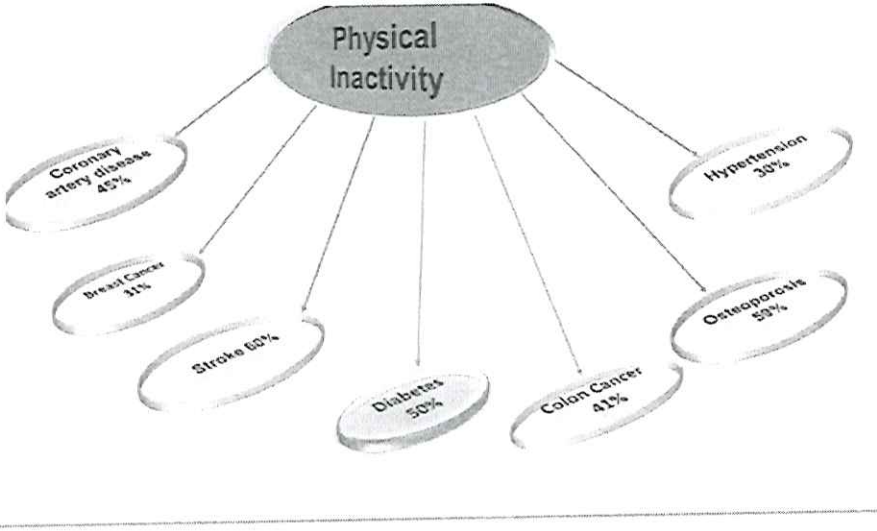
Starvation
Protein



MAJOR METABOLIC PATHWAYS:
- ✓Fatty Acids
- ✓Glucose
- ✓Protein

Biochemical Pathways

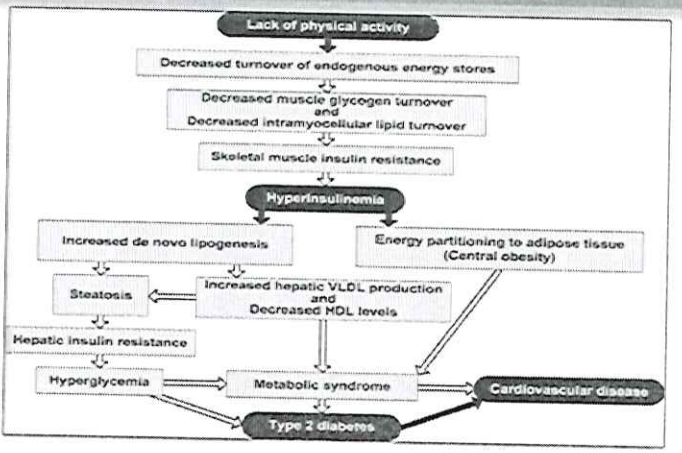


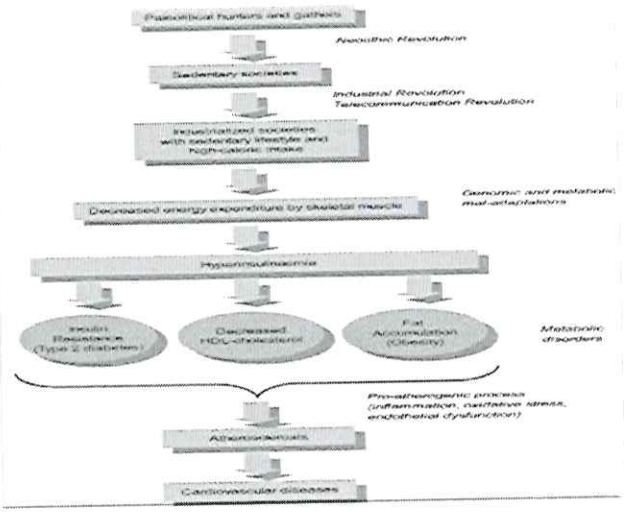


PROBLEMS ASSOCIATED WITH INACTIVITY

- ✓ Decrease in peak consumption of O2 during maximal aerobic exercise
- ✓ Decrease in maximal cardiac output
- ✓ 25% decreases in maximal stoke volume
- ✓ Bones lose mass at 10 times their normal rate
- ✓ Skeletal muscles become weaker with less endurance for light physical effort
- ✓ Muscle lower the capacity to oxidize fatty acids and thus obesity tricks in.
- ✓ Whole body insulin sensitivity declines within the first 3 days of inactivity, whether it is bed rest or active individuals stopping daily exercise.
- ✓ Deep vein thrombosis (DVT) can occur within a time frame as short as an international flight with possible pulmonary thromboembolism in susceptible individuals

CONSEQUENCES OF INACTIVITY



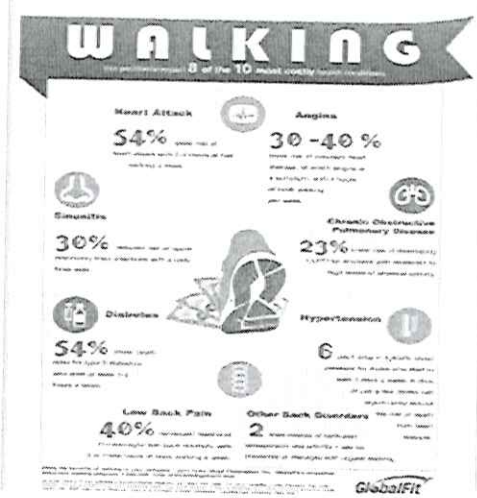


PHYSICAL ACTIVITY

- Physical activity involves the coordinated function of several Physiological and Biochemical systems:
  - ✓ These include the musculo-skeletal system and cardiovascular system
- Within these physiological/Biochemical systems there are signaling and metabolic pathways.
  - ✓ These metabolic pathways are involved in oxidative phosphorylation,
  - ✓ where ATP is synthesized
  - ✓ involving a process that transfers hydrogen to molecular O2,
  - ✓ are responsible for 90% of ATP synthesize in the body

Exercise

- ✓ The BEST Medicine/Pill Which can not be bottled by any Drug company.
- ✓ It is FREE of charge
- ✓ Drugs are very Expensive.
- ✓ Exercise provides All these benefits at NO Cost in Rands but in Sweat to you.

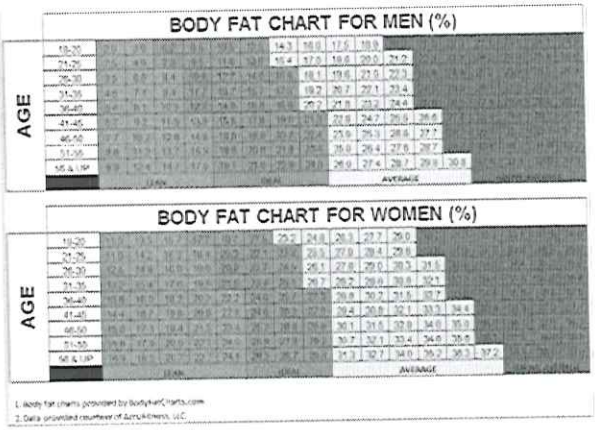


(WHO) WALKING RECOMMENDATION

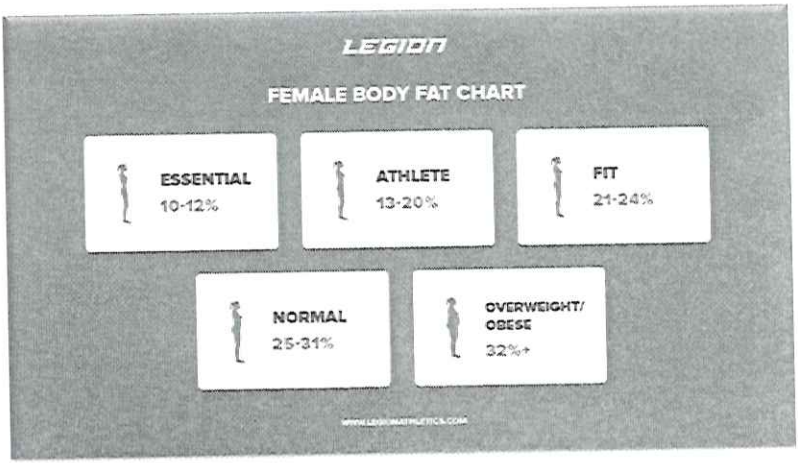
- ❑ 30 Minutes a day
- ❑ 10 000 if you have pedometer
- ❑ 10 min of aerobic exercise

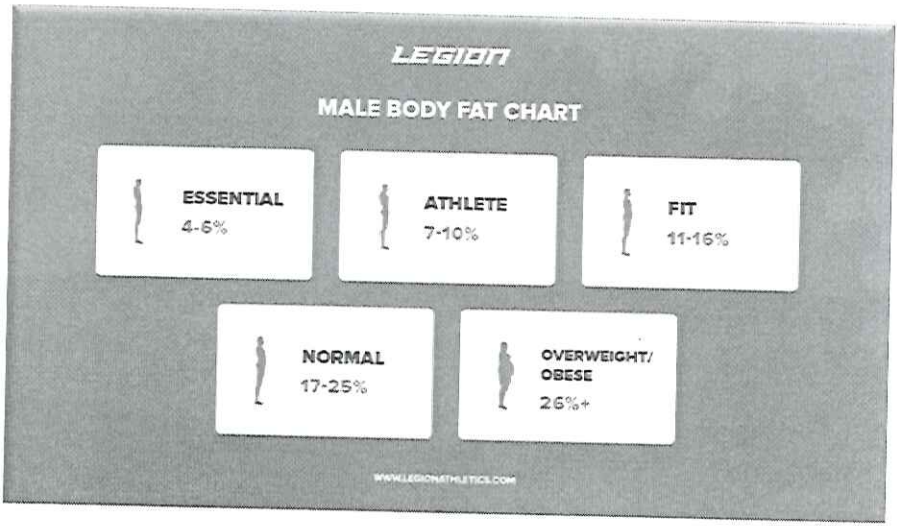
Or in simple terms Exercise to break a SWEAT.

- ❑ This means Activities enough to enough just to break a SWEAT will accrue these benefits
- ❑ This puts a bay Metabolic disorders by 6%
- ❑ The benefits of exercise increase with increase in the workout.
- ✓ Per week its recommended you have burned 500KCal to get these benefits
- ✓ As calories expenditure increase the benefits increases too



1. Body fat charts provided by BodyHealthCharts.com
2. Data provided courtesy of AmeriKinetics, LLC.

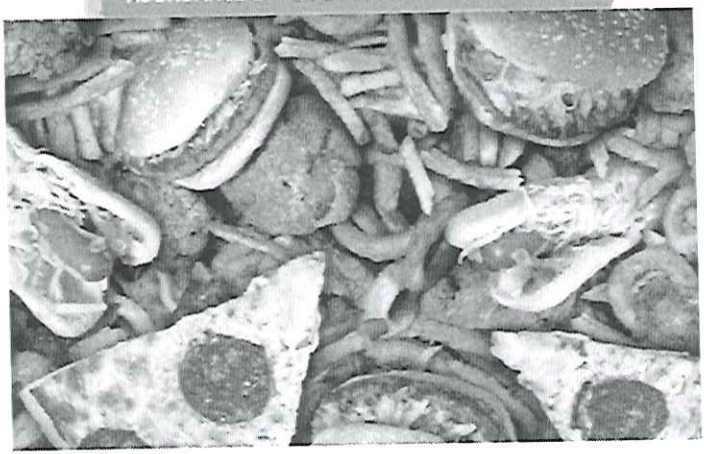




OBESITY

- Its due to excess calorie **Intake** than its **Expenditure**
- Excess Carbohydrates are stored as Glycogen but when its Max is reached they are converted into Fat
- Obesity causes Diabetes, Insulin Resistance, Metabolic Syndrome, Cancer, Hypertension, endometrial, breast, prostate, and colon cancers etc
- Metabolic syndrome: characterized by insulin resistance, excess Triglycerides, inflammation e.g Diabetes, Hypertension, Atherosclerosis, Coronary heart diseases.
- Individuals of these diseases have excess Visceral fat
- Exercise, Metformin etc are used to curb the syndrome

ABUNDANCE OF FOOD IN MOST PARTS OF WORLD



The twitter generations are folding pap like towels:)...hhh look fancy

We are faced with difficult decisions about our health daily, especially choices on food to eat.
In a world with plenty options of Fast food, refined carbohydrates, high sodium content foods we buy.

The healthy food choices is usually not tasty or looking any fancy but dull plate of vegs and fruits.

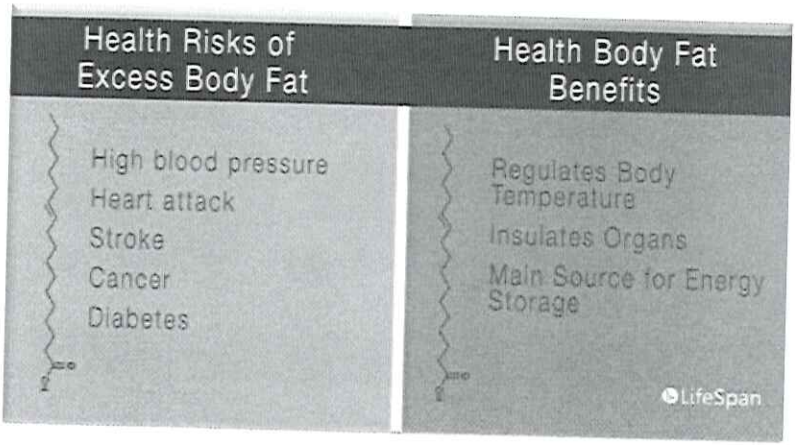


Table 22-2 Fuel Reserves for a Normal 70-kg Man

Fuel	Mass (kg)	Calories[a]
Tissues		
Fat (adipose triacylglycerols)	15	141,000
Protein (mainly muscle)	6	24,000
Glycogen (muscle)	0.150	600
Glycogen (liver)	0.075	300
Circulating fuels		
Glucose (extracellular fluid)	0.020	80
Free fatty acids (plasma)	0.0003	3
Triacylglycerols (plasma)	0.003	30
Total		*166,000*

[a]1 (dieter's) Calorie = 1 kcal = 4.184 kJ.

Source: Cahill, G.E., Jr., *New Engl. J. Med.* 282, 669 (1970).

ITS ALL IN CALORIES & the GENETICS

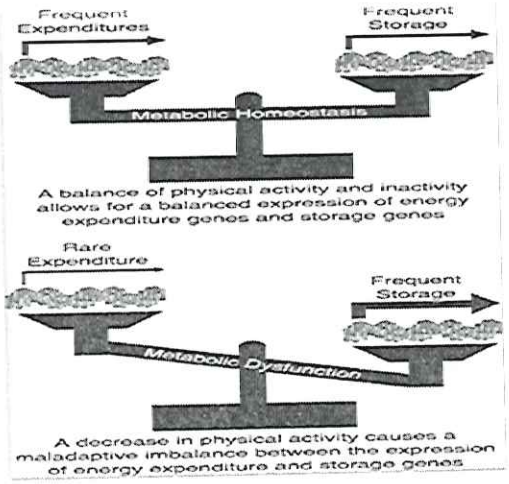
Calories In

Must Equal

Calories Out

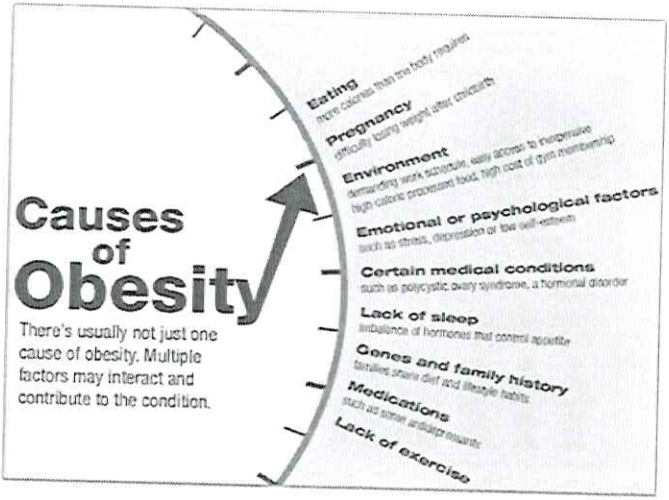
Average needed Calories 1800 - 2500KCal required per Day

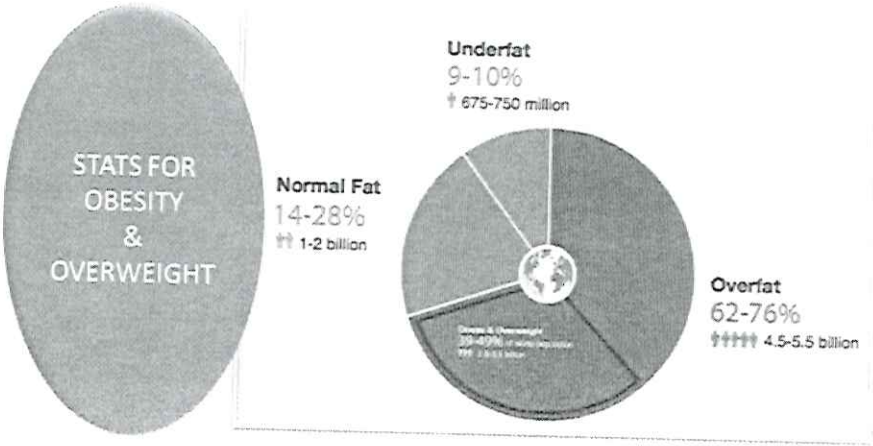
BMR =75%



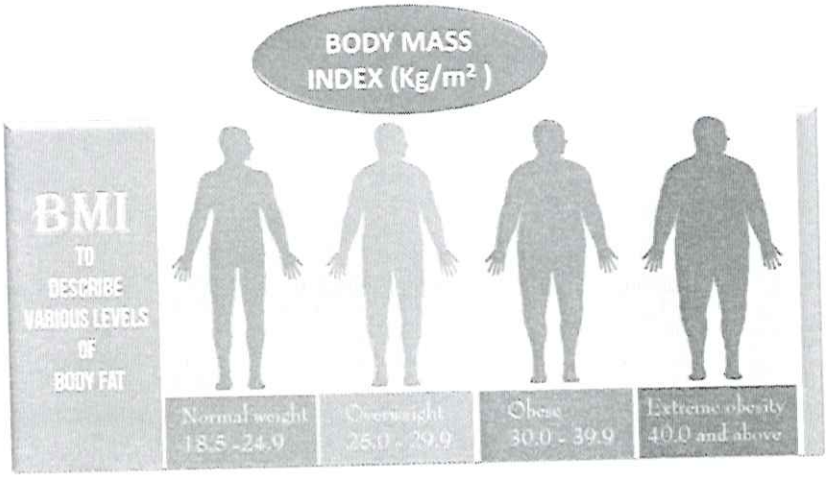
ENERGY EXPENDITURE

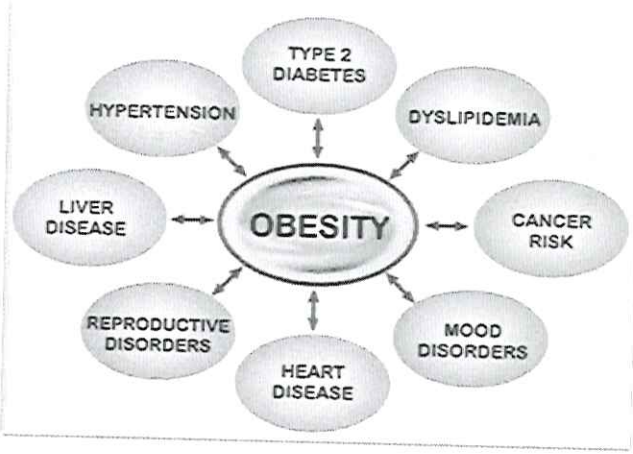
A schematic representation of the balance between gene interactions with physical activity and inactivity on metabolic functioning is shown.
Top: an environment of daily physical activity recapitulates the milieu during natural selection, producing metabolic homeostasis.
Bottom: when physical activity is removed from the environment, there is a loss of an integral environment-gene interaction that causes a maladaptive response leading to multiple metabolic dysfunctions and contributing to many chronic diseases.


Causes of Obesity
There's usually not just one cause of obesity. Multiple factors may interact and contribute to the condition.
Eating
more calories than the body requires
Pregnancy
difficulty losing weight after childbirth
Environment
demanding work schedule, easy access to inexpensive high-calorie processed food, high cost of gym membership
Emotional or psychological factors
such as stress, depression or low self-esteem
Certain medical conditions
such as polycystic ovary syndrome, a hormonal disorder
Lack of sleep
imbalance of hormones that control appetite
Genes and family history
families share diet and lifestyle habits
Medications
such as some antidepressants
Lack of exercise

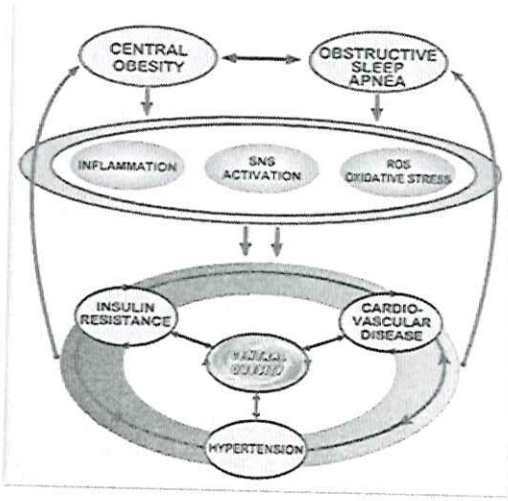

STATS FOR OBESITY & OVERWEIGHT
Normal Fat
14-28%
1-2 billion
Underfat
9-10%
675-750 million
Overfat
62-76%
4.5-5.5 billion


2 IN 3
ADULTS ARE
OVERWEIGHT
OR OBESE


BODY MASS
INDEX (Kg/m²)
BMI
TO
DESCRIBE
VARIOUS LEVELS
OF
BODY FAT
Normal weight
18.5 -24.9
Overweight
25.0 - 29.9
Obese
30.0 - 39.9
Extreme obesity
40.0 and above

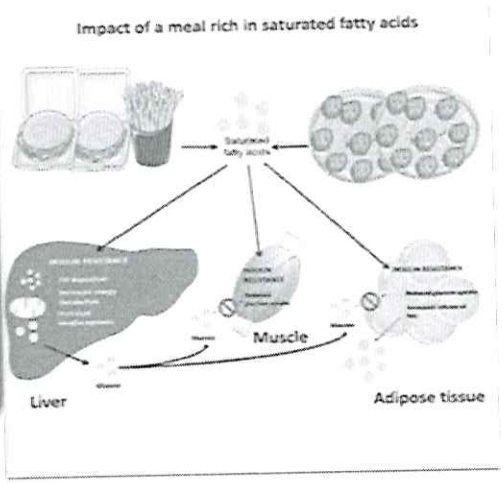


CONSEQUENCES OF CENTRAL OBESITY

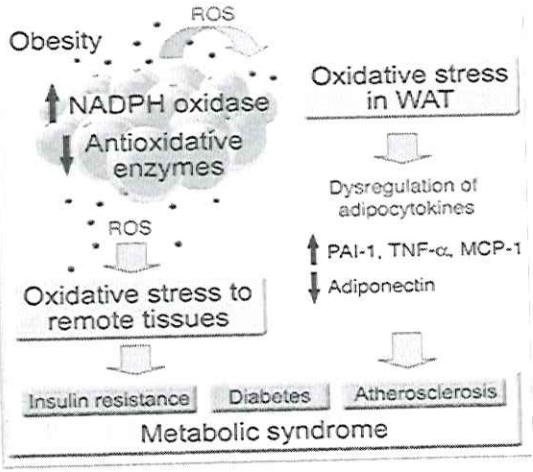


IMPACT OF SATURATED FA

> Intramuscular lipids
> Liver Transport FA to Tissue inducing Insulin Resistance
> Adiposite Formation/Increase

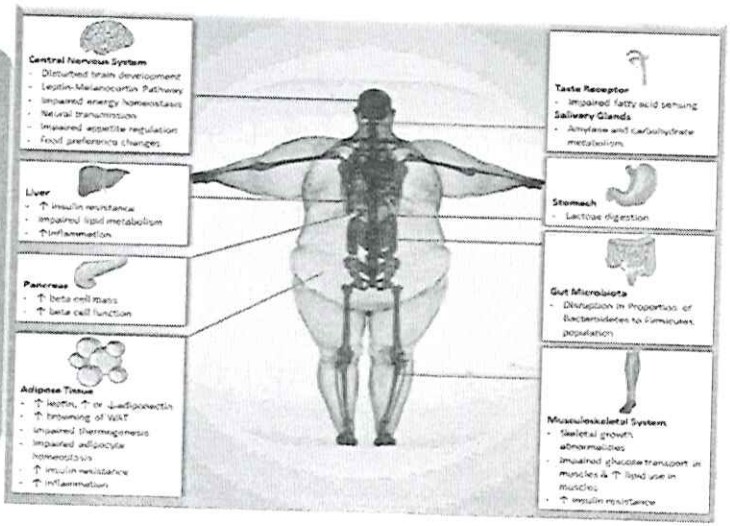


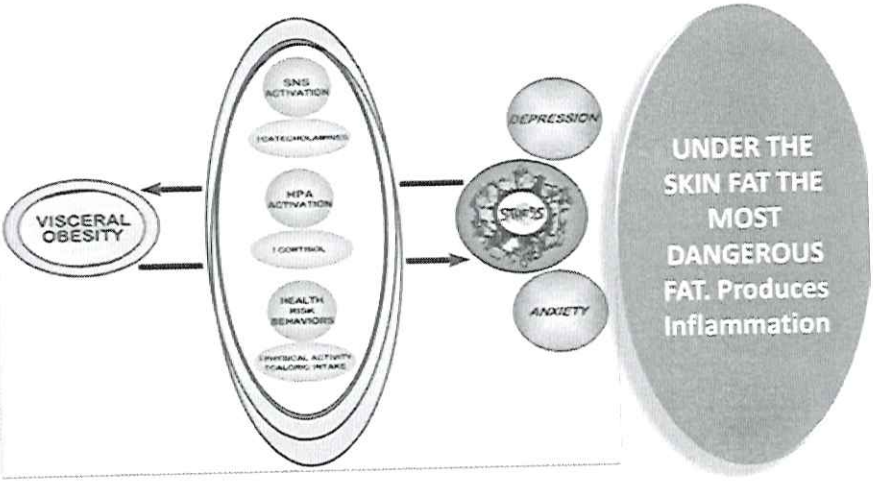
OBESITY RESULTS IN METABOLIC SYNDROME



OBESITY IMPACT ON YOUR HEALTH

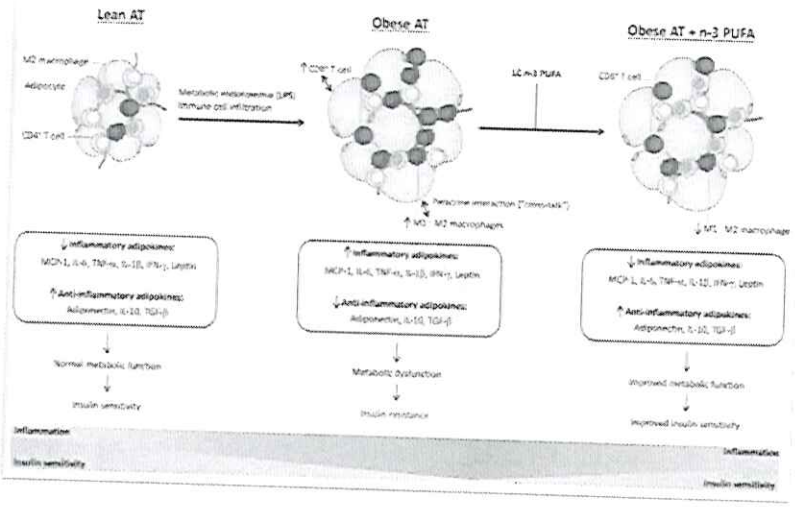
OBESITY Consequences

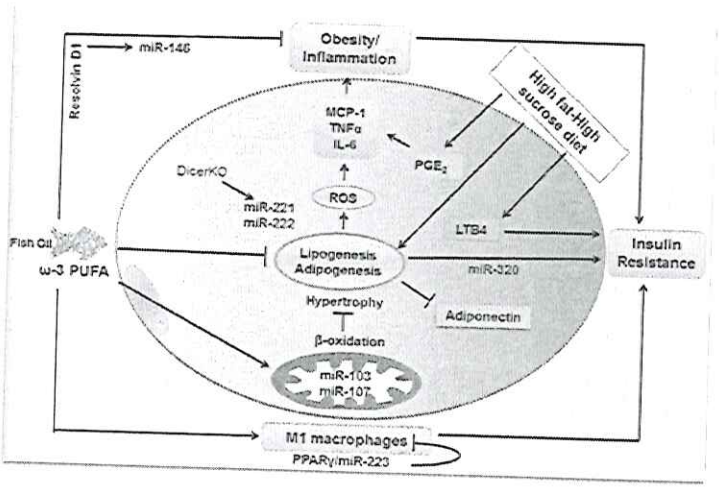


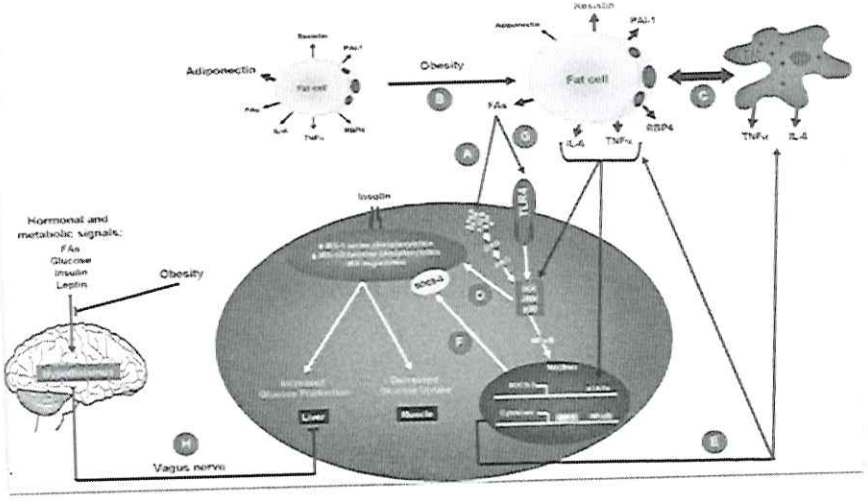


INFLAMMATION

- Excessive Lipids or being Obese results in INFLAMMATION
- Inflammation itself results in DISRUPTION of Metabolic Processes/pathways
- Altered Processes leads to various Ailments such Insulin Resistance, Diabetes, Cardiovascular Diseases, Brain disorders.

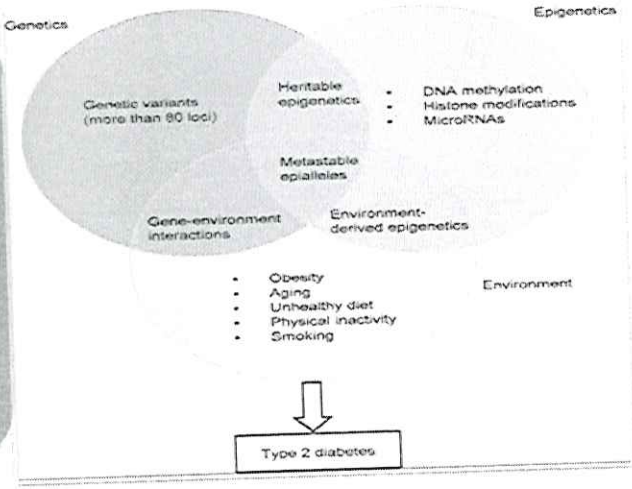

Lean AT
Obese AT
Obese AT + n-3 PUFA
M2 macrophage
Adipocyte
CD4+ T cell
Metabolic endotoxemia (LPS)
Immune cell infiltration
↑ CD8+ T cell
LC n-3 PUFA
CD8+ T cell
Paracrine interaction ("crosstalk")
↑ M1 M2 macrophages
↓ M1 M2 macrophages
↓ Inflammatory adipokines:
MCP-1, IL-6, TNFα, IL-1β, IFNγ, Leptin
↑ Anti-inflammatory adipokines:
Adiponectin, IL-10, TGF-β
↑ Inflammatory adipokines:
MCP-1, IL-6, TNFα, IL-1β, IFNγ, Leptin
↓ Anti-inflammatory adipokines:
Adiponectin, IL-10, TGF-β
↓ Inflammatory adipokines:
MCP-1, IL-6, TNFα, IL-1β, IFNγ, Leptin
↑ Anti-inflammatory adipokines:
Adiponectin, IL-10, TGF-β
Normal metabolic function
Insulin sensitivity
Metabolic dysfunction
Insulin resistance
Improved metabolic function
Improved insulin sensitivity
Inflammation
Insulin sensitivity
Inflammation
Insulin sensitivity


Resolvin D1
miR-146
Obesity/
Inflammation
High fat-High sucrose diet
MCP-1
TNFα
IL-6
PGE2
DicerKO
miR-221
miR-222
ROS
LTB4
Fish Oil
ω-3 PUFA
Lipogenesis
Adipogenesis
miR-320
Insulin
Resistance
Hypertrophy
Adiponectin
β-oxidation
miR-103
miR-107
M1 macrophages
PPARγ/miR-223

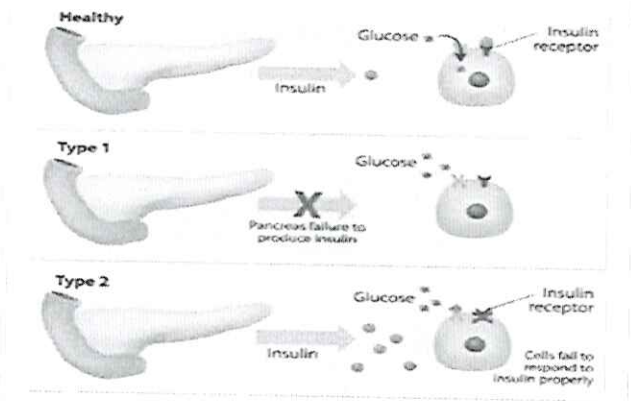


TYPE 2 DIABETES

[Constitutes >90%] of All Diabetes cases.

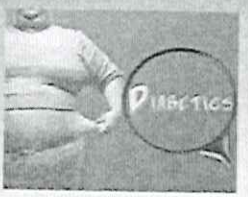


DIABETES MELLITUS



TYPE 2 DIABETES

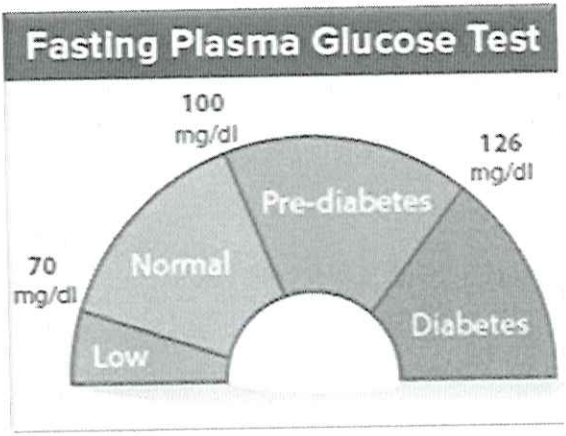
- Most common
- >40 years of age
- Normal or overweight
- Genetic factor
  - Strongly positive

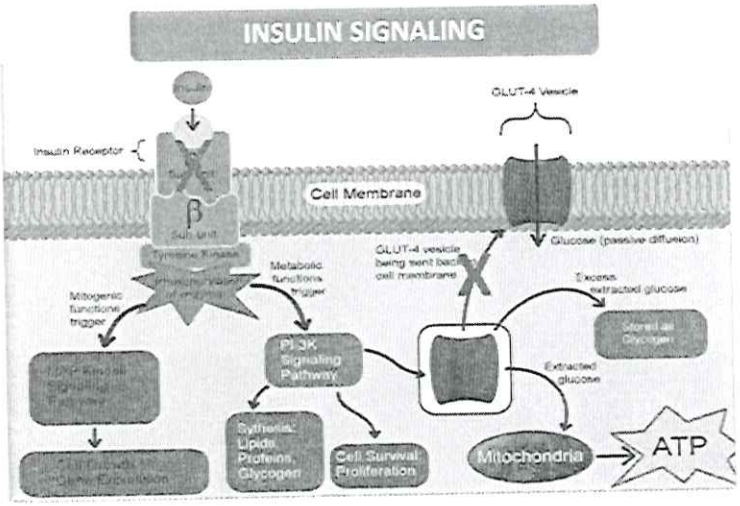


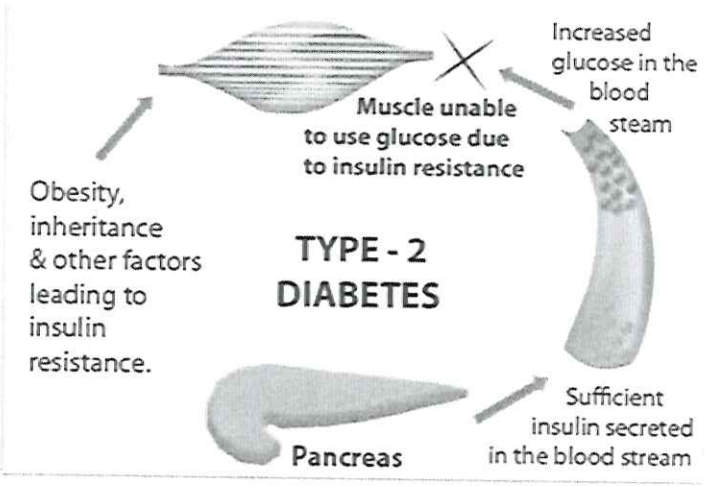
Non Diabetic (No Family History)

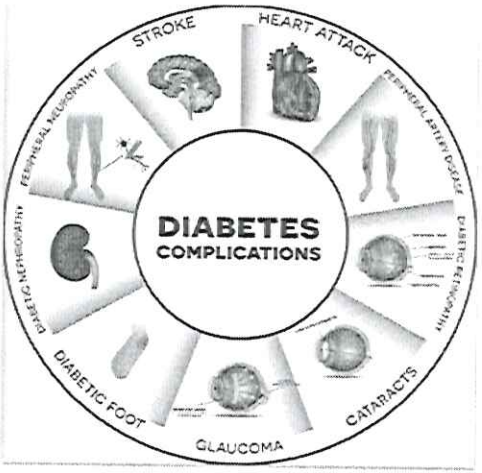
Non Diabetic (With Family History)

Diabetic

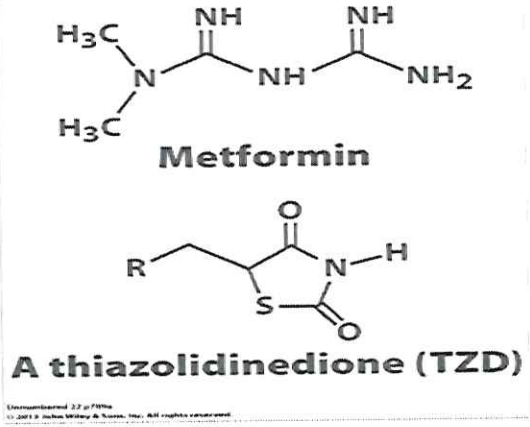

Fasting Plasma Glucose Test
100
mg/dl
126
mg/dl
Pre-diabetes
70
mg/dl
Normal
Diabetes
Low

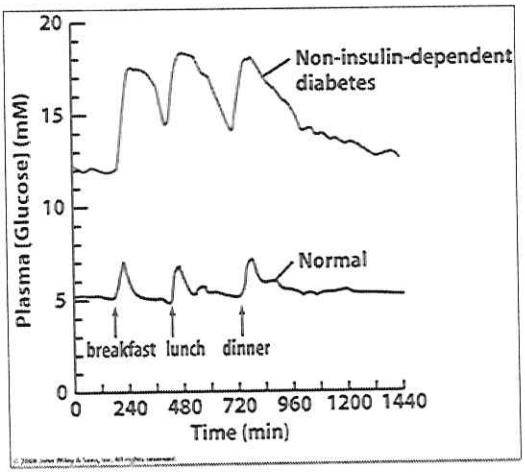

INSULIN SIGNALING
Insulin
GLUT-4 Vesicle
Insulin Receptor
Cell Membrane
β
Sub unit
Glucose (passive diffusion)
Metabolic functions trigger
GLUT-4 vesicle being sent back to cell membrane
Excess extracted glucose
Mitogenic functions trigger
PI-3K Signaling Pathway
Stored as Glycogen
Extracted glucose
Synthesis: Lipids, Proteins, Glycogen
Cell Survival Proliferation
Mitochondria
ATP


Increased glucose in the blood steam
Muscle unable to use glucose due to insulin resistance
Obesity, inheritance & other factors leading to insulin resistance.
TYPE - 2 DIABETES
Sufficient insulin secreted in the blood stream
Pancreas


STROKE
HEART ATTACK
PERIPHERAL ARTERY DISEASE
DIABETIC RETINOPATHY
CATARACTS
GLAUCOMA
DIABETIC FOOT
DIABETIC NEPHROPATHY
PERIPHERAL NEUROPATHY
DIABETES COMPLICATIONS

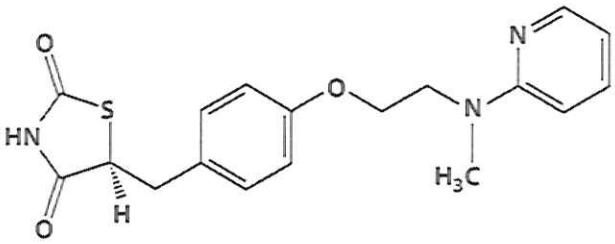
Drugs Decrease Insulin Resistance





Diabetes a 3rd leading cause of death in the US after Heart disease & cancer.
2 types of diabetes:
1. Insulin dependent and Non insulin dependent (>90%).
Drugs such as Metformin & TZD are used.

Some Increase Risk of Heart Attack & Stroke



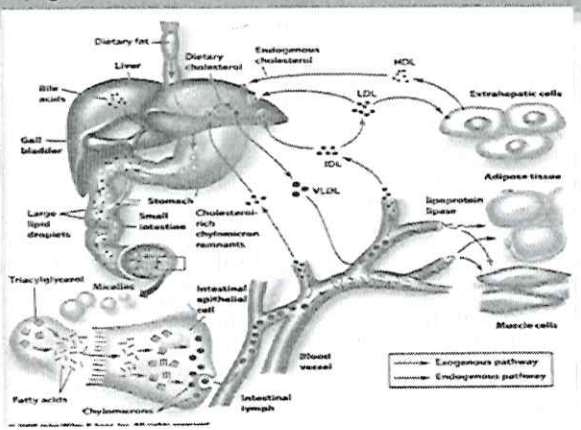
Rosiglitazone (Avandia)

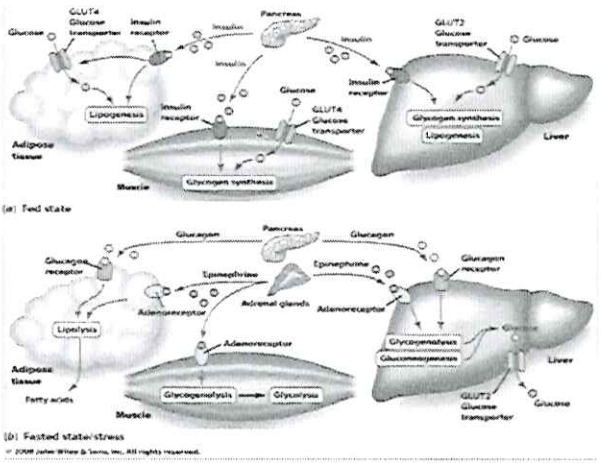
THE FAT PROBLEM

Three major biological functions

1. Essential component of biological membranes forming lipid-bilayer
2. Lipid containing hydrocarbons serve as energy source
3. Many intra- and intercellular signaling events involve lipid molecules. E.g inositol, phospholipids

Plasma triacylglycerol & cholesterol transport in humans



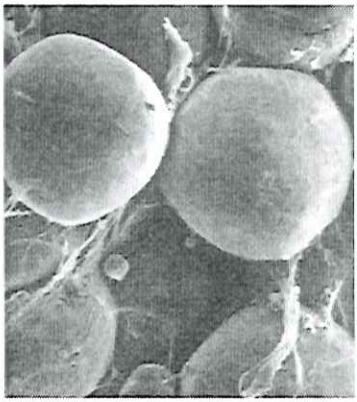


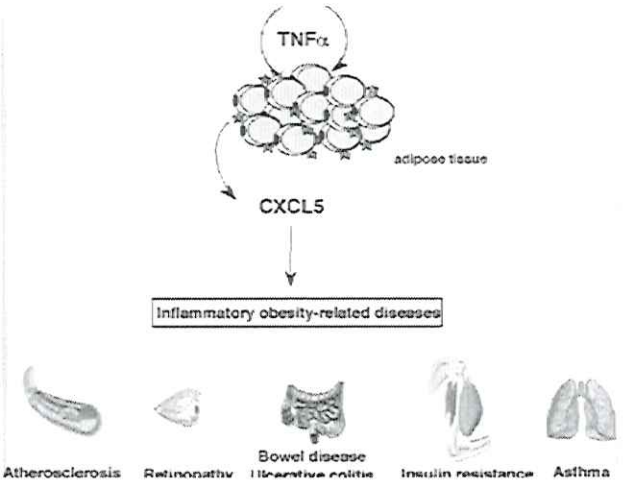
COMPARISON OF METABOLISM IN

a) Fed (abundance of energy)

b) Starvation (Scarcity of energy)

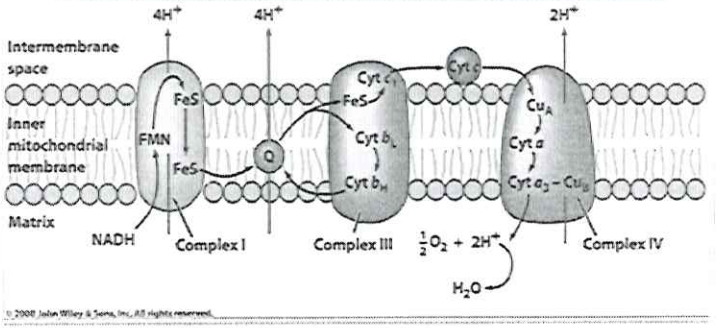
Adipocytes Containing Fat Globule



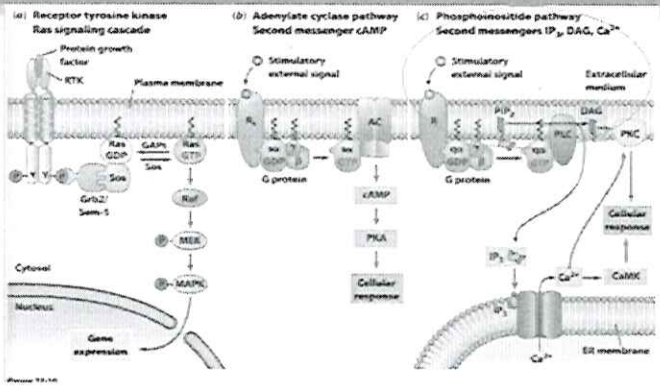


LIPIDS PLAY VITAL ROLE IN MEMBRANE FORMATION

CRITICAL IN MANY PATHWAYS e.g ATP synthesis



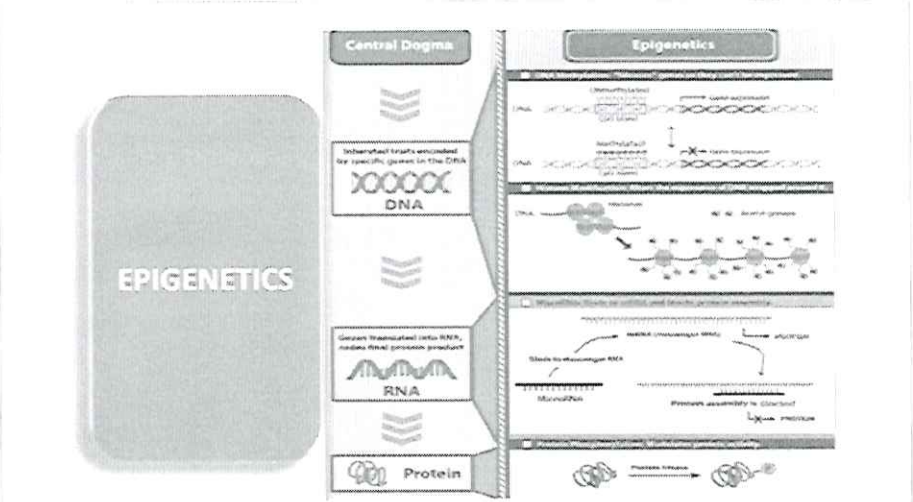
LIPIDS play vital role in Signal Transduction Pathways

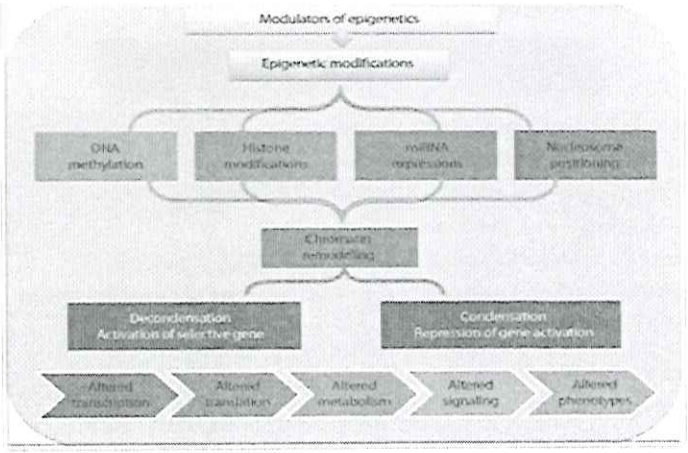


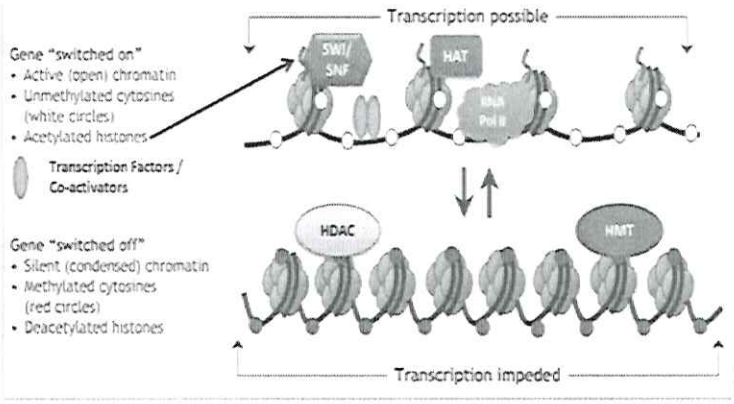
Metabolic Homeostasis

AMPK-The Cell Fuel Gauge

- It activates Glycolysis in cardiac muscle
- Inhibits Lipogenesis & gluconeogenesis in liver
- Promotes fatty acid oxidation & glucose uptake in muscle
- Inhibits Lipolysis in adipocytes
- AMPK is regulated by adiponectin hormone found in adipocytes.
- Leptin also controls metabolism as a satiety hormone by promoting energy expenditure.
- Leptin resistance lead to increase of Neuropeptide Y which stimulate appetite & fat accumulation (Inhibited by Leptin+Insulin)
- Grehlin is an appetite stimulating hormone secreted by empty stomach


EPIGENETICS
Central Dogma
DNA
RNA
Protein
Epigenetics


Modulators of epigenetics
Epigenetic modifications
DNA methylation
Histone modifications
miRNA repressions
Nucleosome positioning
Chromatin remodelling
Decondensation
Activation of selective gene
Condensation
Repression of gene activation
Altered transcription
Altered translation
Altered metabolism
Altered signaling
Altered phenotypes

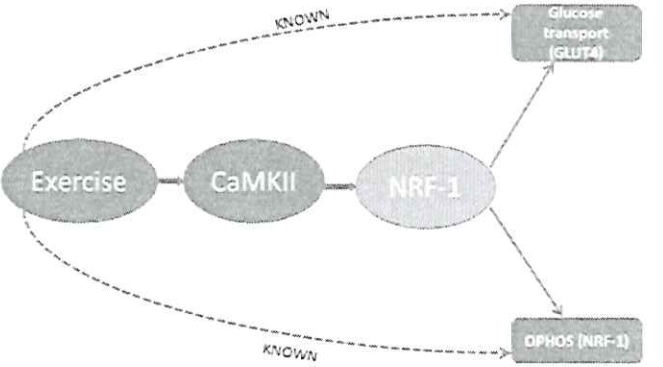


HOW DOES EXERCISE PROTECT INDIVIDUALS FROM OBESITY & DIABETES?

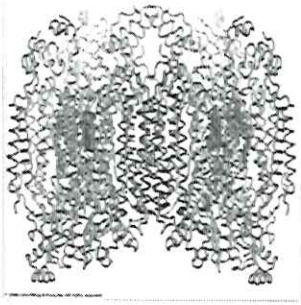
Exercise protects individuals from type 2 diabetes

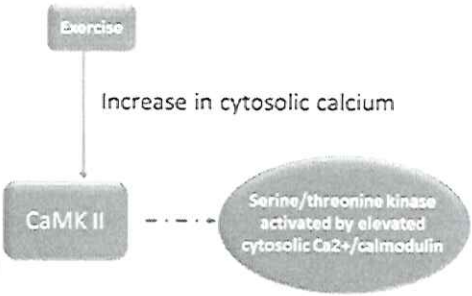
Delays/Prevents the onset of T2D/Obesity

Our Hypothesis Model



CaMKII is activated by exercise





Mechanisms by which exercise protect individuals.

- Increases in Glucose transport- GLUT4 protein.
- Increases in mitochondrial oxidative capacity-NRF-1.
- By remodeling the chromatin increasing NRF-1 epigenetics
- The result is increased expression of genes & protects individuals from these ailments.

The GLUT4 Protein

- Insulin responsive protein
- The major glucose transporter in skeletal muscle.
- Essential in glucose transport

Blood glucose

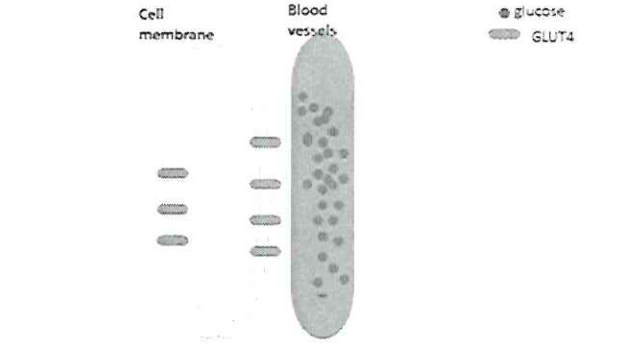
Glucose transporters

Name	Location	Insulin
GLUT1	skeletal muscle, brain, erythrocytes,	No
GLUT2	liver, pancreas, kidney, intestine	No
GLUT3	Brain	No
GLUT4	skeletal muscle, heart, brain, adipose	Yes

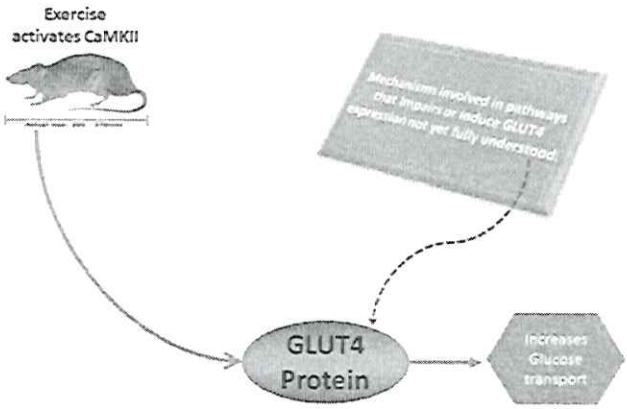
cemia Hyperglycemia

6 8 10 12.....mmol/L

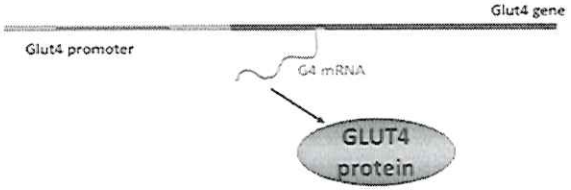
Glucose transport by GLUT4 protein



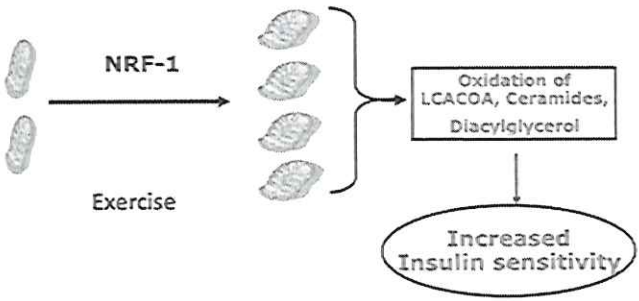
Signals that induce GLUT4 expression



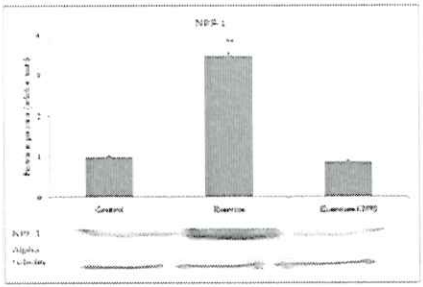
Regulation of the *Glut4* gene expression



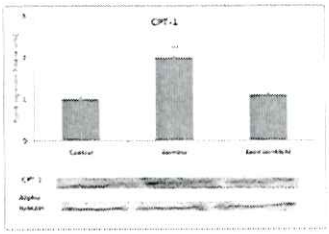
NRF-1, the mitochondrial transcription factor

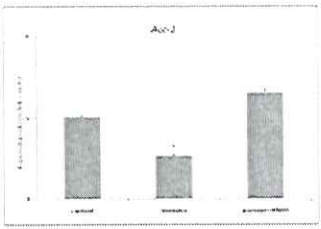


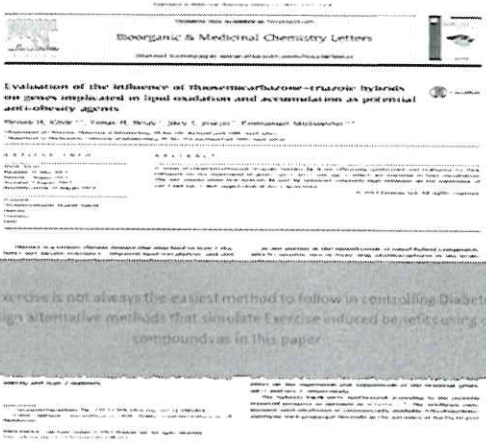
CaMKII regulate NRF-1



CaMKII regulate lipid metabolizing genes







Bioorganic & Medicinal Chemistry Letters

Evaluation of the influence of thiocarbazone–fluoxetine hybrids on genes implicated in lipid oxidation and accumulation as potential anti-obesity agents

Although Exercise is not always the easiest method to follow in controlling Diabetes, we want to design alternative methods that simulate Exercise induced benefits using organic compounds as in this paper

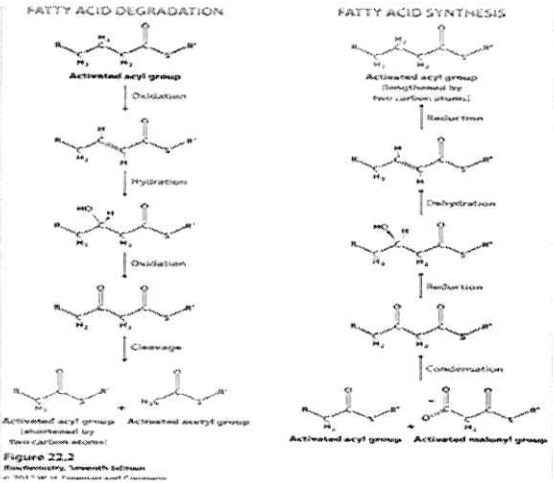
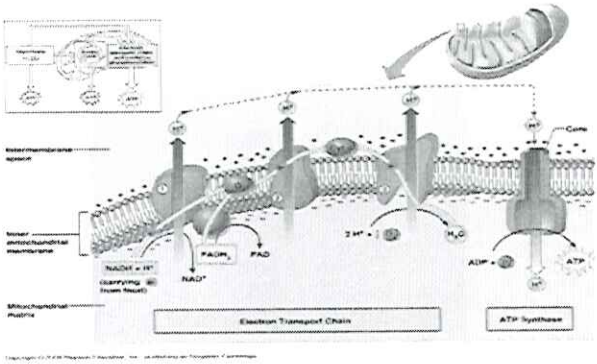


Figure 22.2
Biochemistry, Seventh Edition

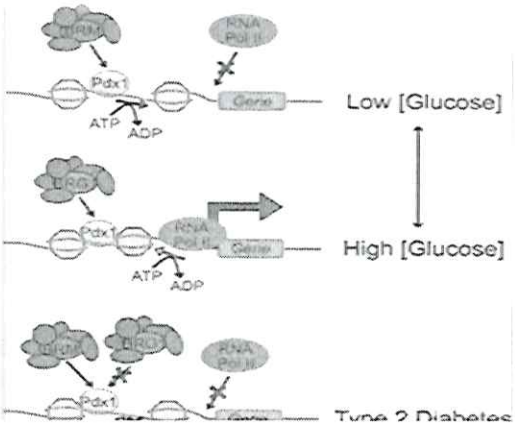
ETC (electron transport chain)



THERE EXCESSIVE CARBOHYDRATE IN OUR MODERN DIET.
CHO ARE CONVERTED TO FATS.

EXCESS GLUCOSE/CARBPHYDRATES LEADS TO METABOLIC DOSRDERS

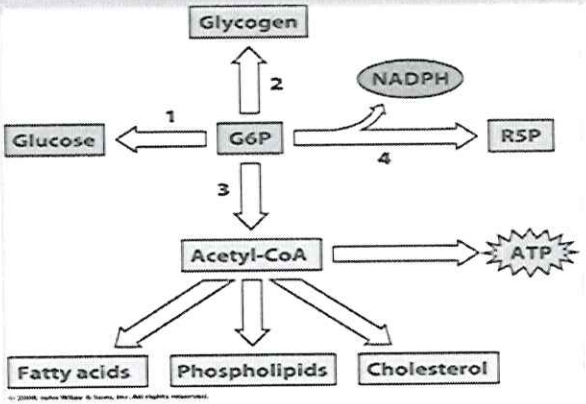
SUGAR ALTERS GENE TRANSCRIPTION

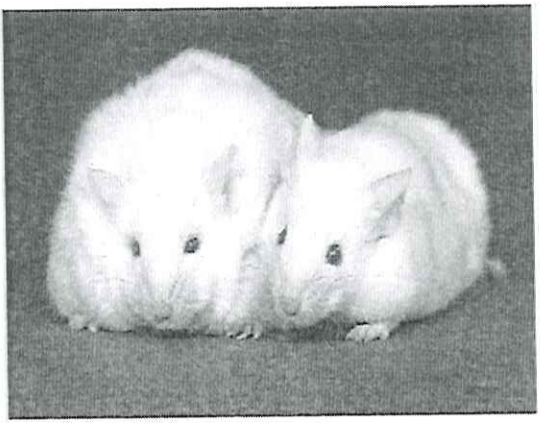


The results of altered gene transcription:

- ✓ Silencing critical genes that protects individuals from many diseases.

G-6-P crossroad of carbohydrate metabolism





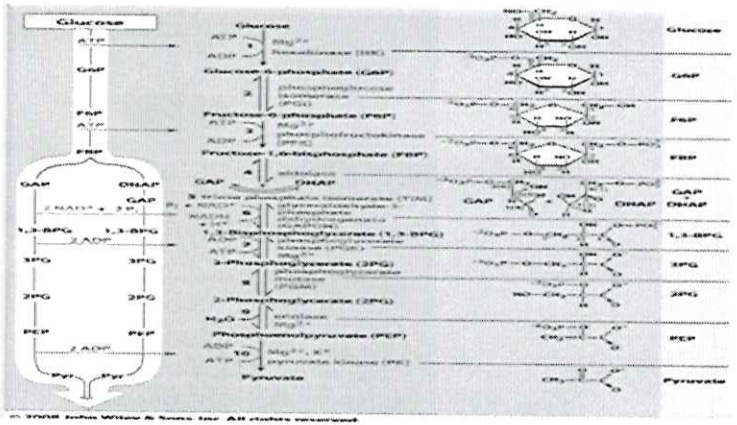
Chapter 22 Opener part 1

ENERGY STORAGE

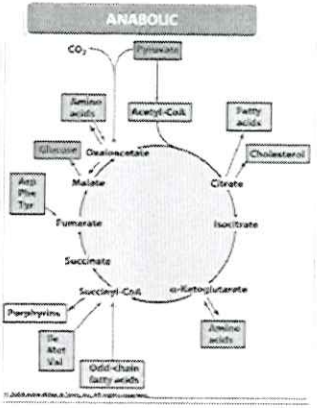
Fat accumulation- a way of storing energy for later use.

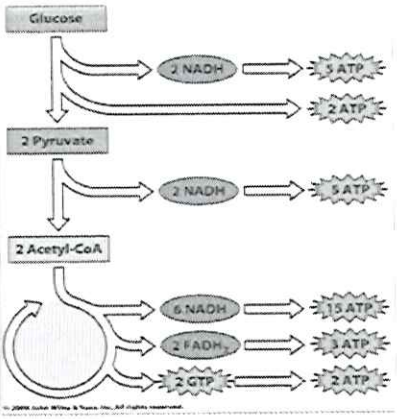
1. Fatty acid synthesis-For energy storage
2. Fatty acid degradation- for energy use.
3. Two pathways are reverse of each other.

GLYCOLYSIS OVERVIEW



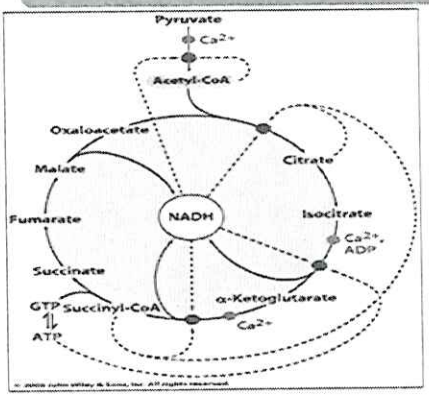
TCA an AMPHIBOLIC pathway





ENERGY IS A TIGHTLY CONTROL PROCESS LEADING TO ON AND OFF ATP SYNTHESIS

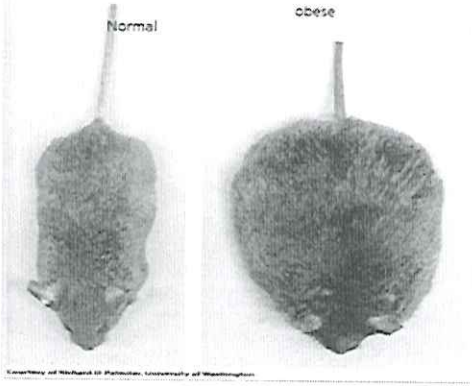
Regulation of the Citric Acid Cycle



1. PDH
2. Citrate synthase.
3. NAD Isocitrate dehydrogenase.
4. Ketoglutarate dehydrogenase

1. Substrate availability
2. Product inhibition (Citrate & OAA)
3. Competitive feedback inhibition

The effect of obese gene knockout

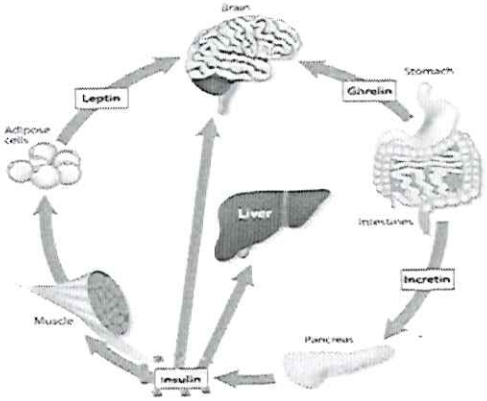


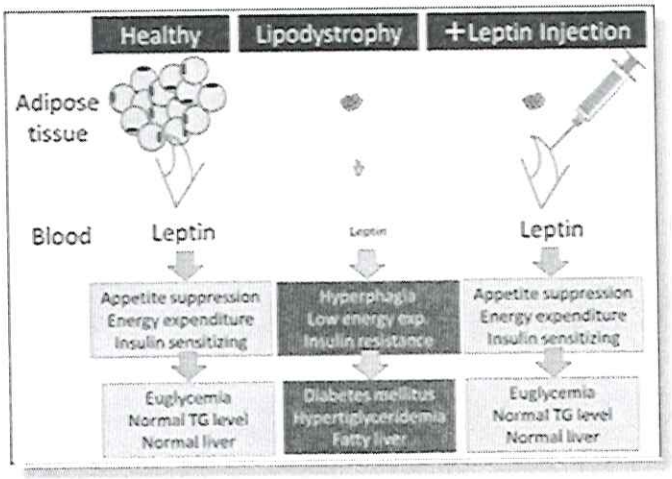
- Obese gene codes for leptin.
- Its lack leads to overeating.
- Excess energy is stored as fat & glycogen in the body for future use
- Persistent excess calories leads to obesity.

Hormones Play key Role in Controlling Metabolism

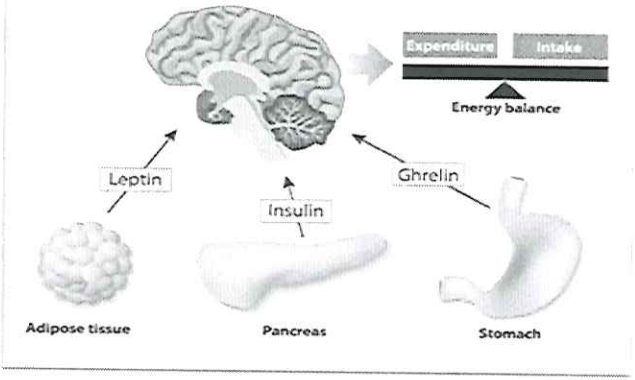
1. Leptin = Regulate Appetite
2. Adiponectin regulate Glucose & Lipids

APPETITE & HUNGER
(hormones)



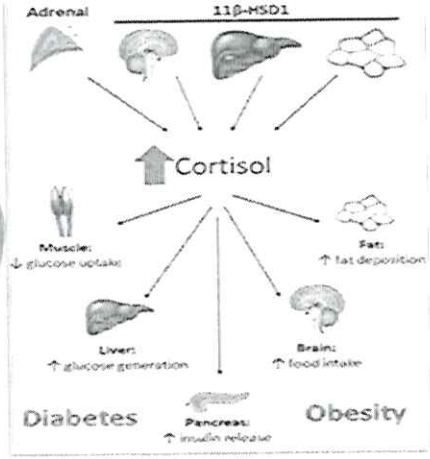


CONTROL OF FOOD INTAKE



CORTISOL IS INCREASED BY STRESS KILLING LOT OF PEOPLE

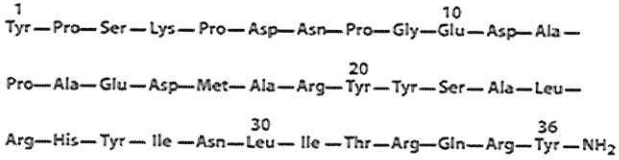
IMPACT OF CORTISOL ON DIABETES & OBESITY



Neuropeptide Y

-stimulates appetite and is released by the Hypothalamus

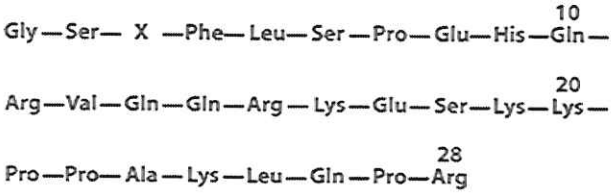
- Diminished response to Leptin results to high Neuropeptide



Neuropeptide Y
(The C-terminal carboxyl is amidated)

Ghrelin

Appetite stimulating hormone secreted by empty stomach



Ghrelin
(X = Ser modified with *n*-octanoic acid)

PYY

An appetite suppressing hormone found in the GIT

3 10
Ile — Lys — Pro — Glu — Ala — Pro — Gly — Glu —

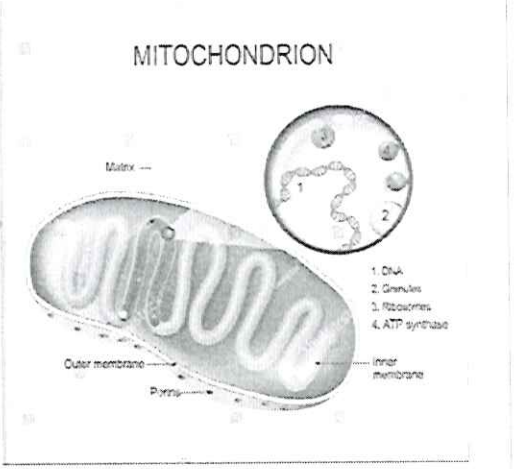
20
Asp — Ala — Ser — Pro — Glu — Glu — Leu — Asn — Arg — Tyr —

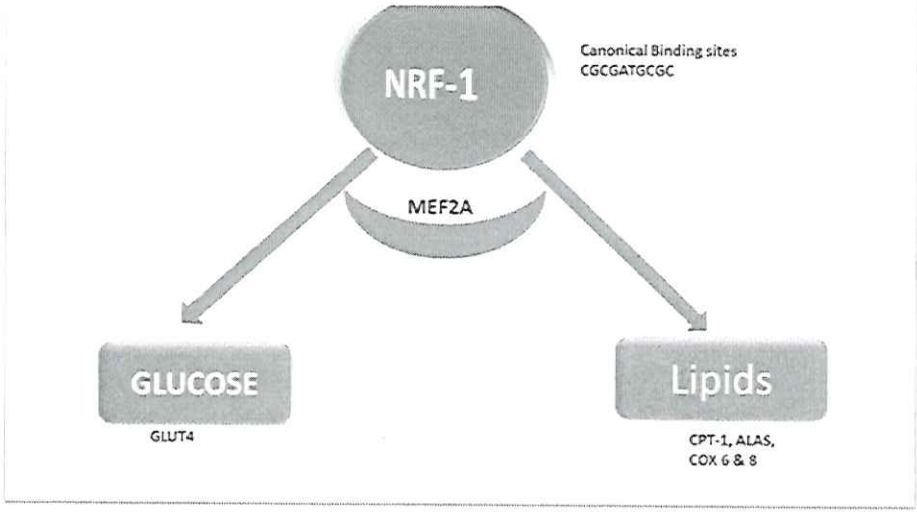
30
Tyr — Ala — Ser — Leu — Arg — His — Tyr — Leu — Asn — Leu —

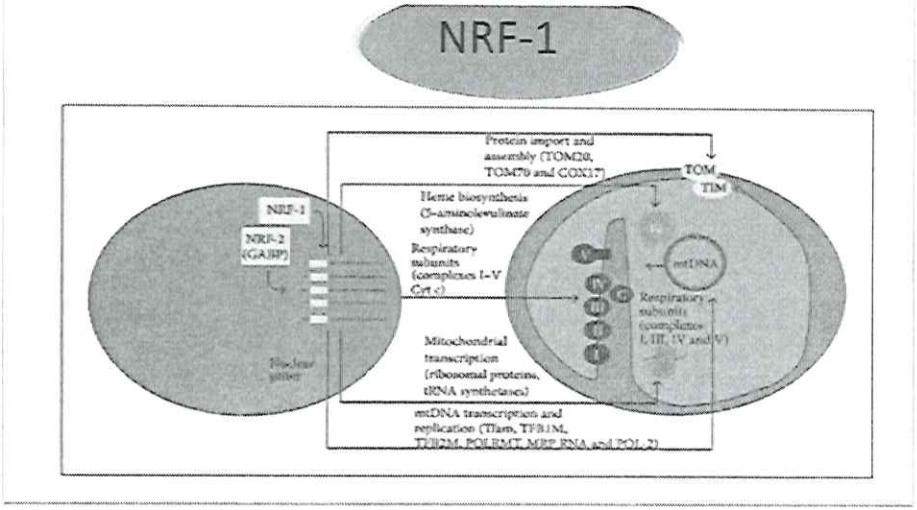
36
Val — Thr — Arg — Gln — Arg — Tyr

PYY_{3-36}

NRF-1



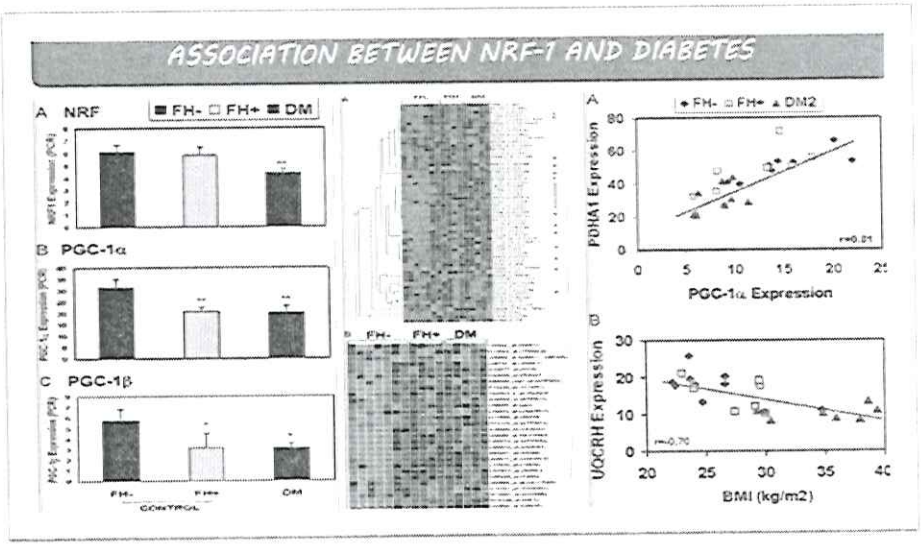

NRF-1
Canonical Binding sites
CGCGATGCGC
MEF2A
GLUCOSE
GLUT4
Lipids
CPT-1, ALAS,
COX 6 & 8


NRF-1
Protein import and assembly (TOM20, TOM70 and COX17)
TOM
TIM
Heme biosynthesis (δ-aminolevulinate synthase)
NRF-1
NRF-2 (GABP)
Respiratory subunits (complexes I-V Cyt c)
mtDNA
Respiratory subunits (complexes I, III, IV and V)
Mitochondrial transcription (ribosomal proteins, tRNA synthetases)
mtDNA transcription and replication (Tfam, TFB1M, TFB2M, POLRMT, MRP RNA and POL-γ)

Changes in Insulin Sensitivity and Muscle Oxidative Capacity Kevin R. Short., 2003

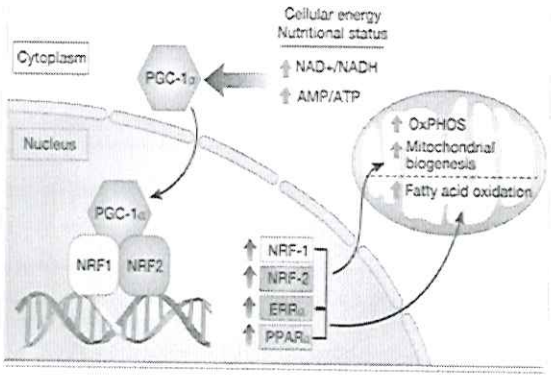
1. **Aerobic capacity** decrease 10% per Decade
   As measured by VO2peak declined linearly with age
2. **Insulin sensitivity** decrease 8% per Decade

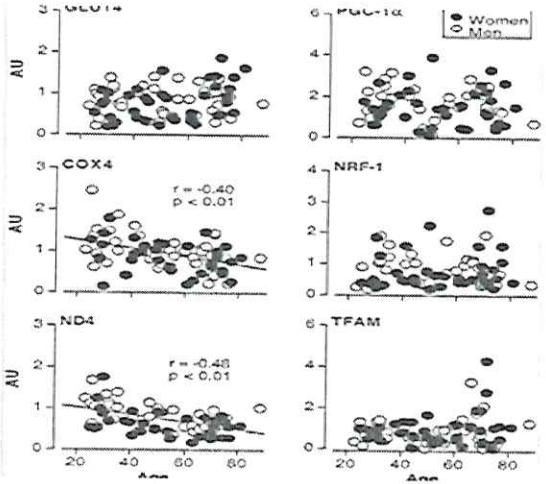
Insulin resistance increases and muscle oxidative capacity decreases during aging, but lifestyle changes—especially physical activity—may reverse these trends



NRF-1 = Nuclear Respiratory Factor 1

- Nuclear respiratory factor 1 (NRF-1) encodes a protein that homodimerizes and functions as a transcription factor which activates the expression of some key metabolic genes regulating cellular growth and nuclear genes required for respiration, heme biosynthesis, and mitochondrial DNA transcription and replication.





MITOCHONDRIAL GENE EXPRESSION IN RESPONSE TO EXERCISE BOTH IN MEN AND WOMEN

NRF-1 = Nuclear Respiratory Factor -1

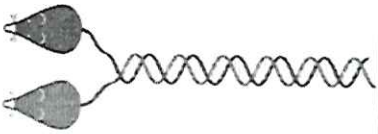
- Transcription Factor For Mitochondrial Biogenesis
- Control Genes involved in OXPHOS Oxidative Phosphorylation
- Most genes involved metabolism have NRF-1 binding sites
- Now it is known to involved in Glucose Metabolism
- Thus in control both Lipids and Glucose in parallel
- Directly links it to Metabolic Disorders such Diabetes & Obesity

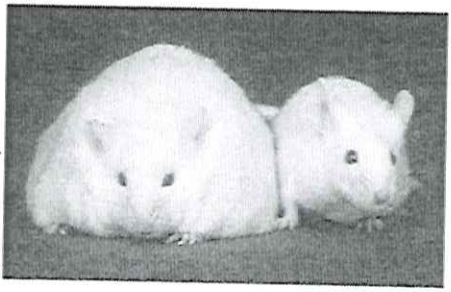
Methods We Employ

- Western Blotting = Protein expression
- Qpcr = Gene expression
- LC/GC-MS – We assess lipid species metabolites
- Chromatin Immunoprecipitation = assess Transcription binding to Cis/Trans Elements
- Accessibility Asssay to assess DNA/Protein accessibility
- Cloning
- Mammalian Cell culture- C2C12, Hepatocytes, Adipocytes
- Animal models – Rats and Mice

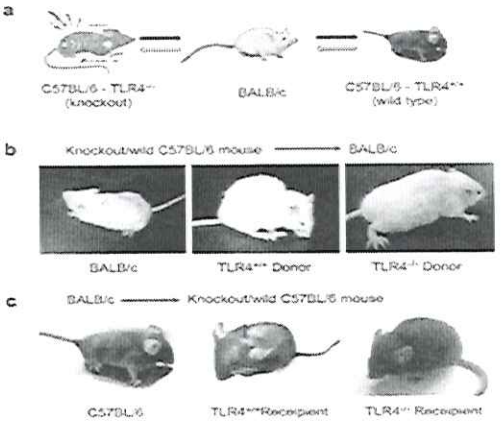
RATS WONDERFUL EXPERIMENTAL TOOL IN MEDICINE, BIOCHEMISTRTY & PHYSIOLOGY

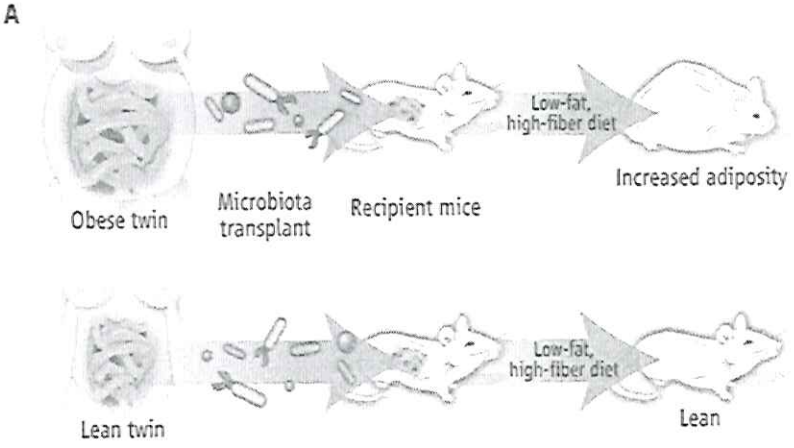
They provide us vital tools in elucidating pathways/mechanisms involved Leading Diabetes and Obesity.
These provide with information to develop Therapeutics for these Metabolic disorders. Especially in the Chromatin where our focus is at.





Various Rats and Mice models and how we can manipulate their genetics, altering or overexpressing various genes in them





Questions

- Does NRF-1 bind the *Mef2a* gene & increase its expression?

- Does the increase in MEF2A result in increased binding to the *Glut4* gene?

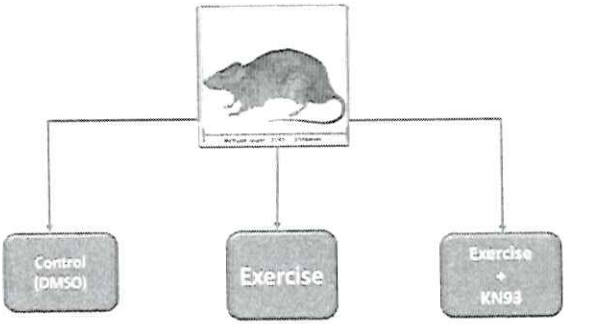
Experimental Design

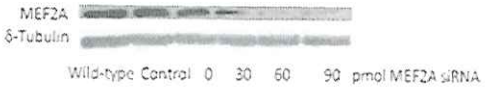
- ChIP assay to detect acetylation & binding.
  - NRF-1/*Mef2A*
  - MEF2A/*Glut4*
  - NRF-1/*Alas*

GLUT4 EXPRESSION

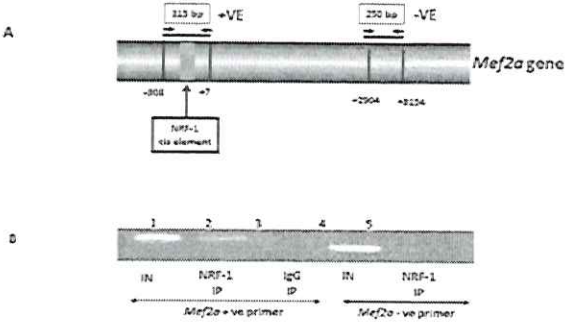
MITOCHONDRIAL EXPRESSION

Methodology

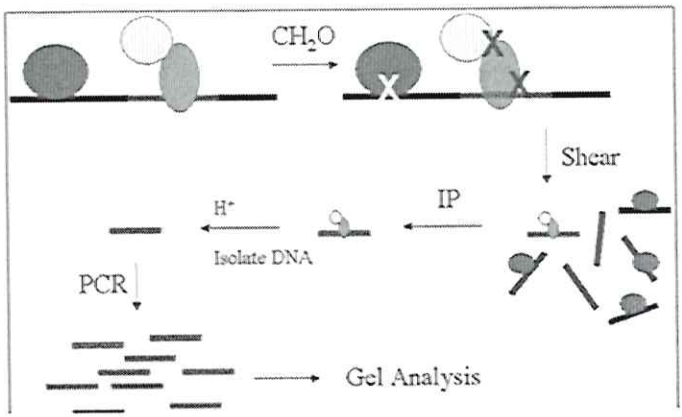




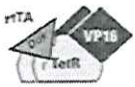
Primer design for *Mef2a* gene

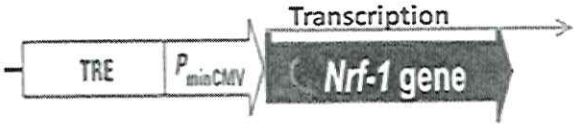


CHROMATIN IMMUNOPRECIPITATION

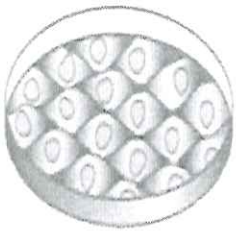


Tet-On gene expression system



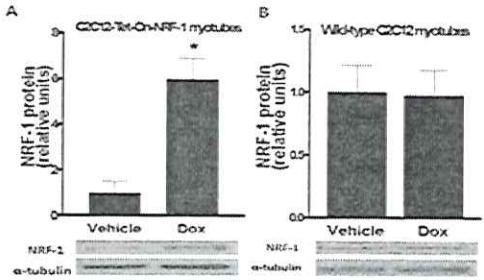


MEF2A RNA Interference

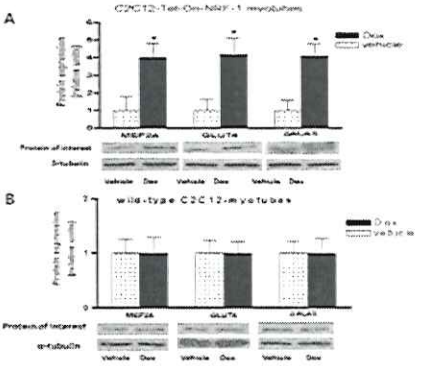


C2C12-Tet-On-NRF-1

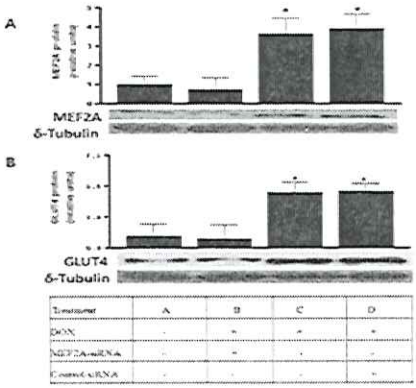
Overexpression of NRF-1



Overexpression of NRF-1

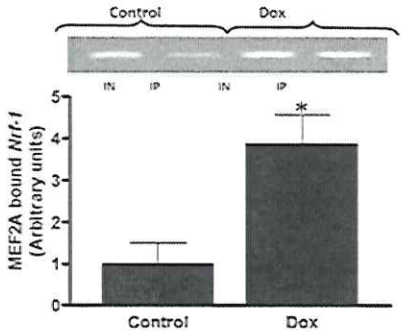


Effect of MEF2A silencing on NRF-1 overexpression

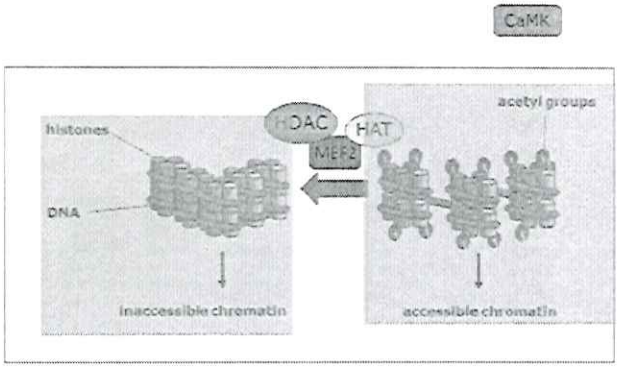


Treatment	A	B	C	D
DOX	-	+	+	+
MEF2A-siRNA	-	+	-	-
Control-siRNA	-	-	-	+

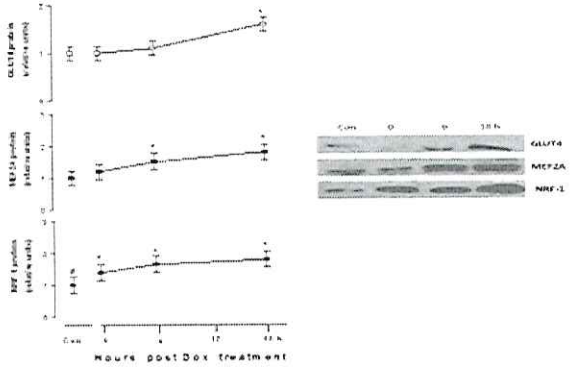
Dox increases NRF-1 binding to the *Mef2a* gene

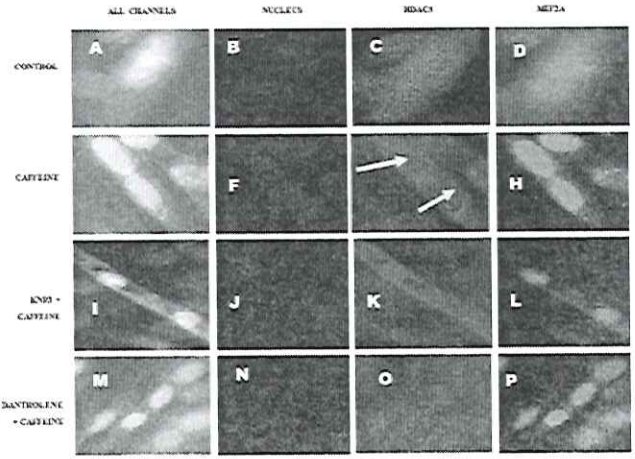


Chromatin remodeling: CaMKII

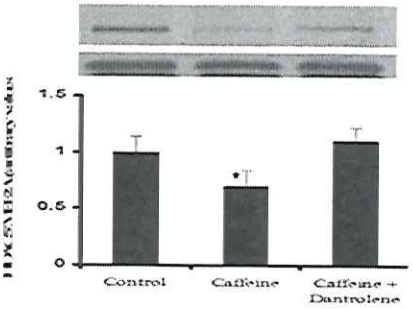


Time line analysis of NRF-1 overexpression

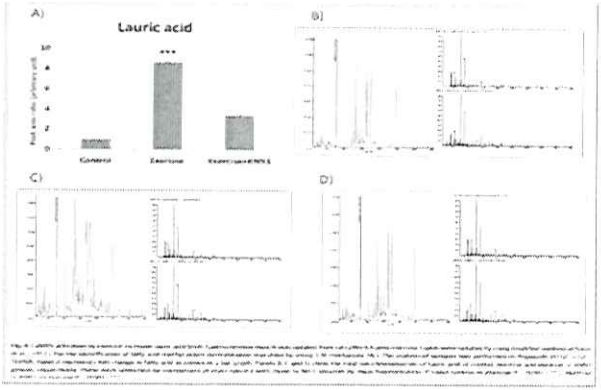




CaMKII activation exports HDAC5



CaMKII activation increases Lauric acid



IN PERORATION

- Humans likely have the potential for the most advantageous environment-gene interaction in their history on Earth; we are quite fortunate to be alive in this era.
- In a period of less than a half-century, knowledge has advanced from Watson and Crick (97) to a complete sequence of the human genome.
- However, humans physical inactivity into their lifestyle has had the adverse effect of increasing the incidence of inactivity-induced chronic disease.
- The solution to this critical societal problem lies in a more advanced understanding of the ***maladaptations due to physical inactivity-gene interactions***.
- Understanding ***physical inactivity-gene interactions and impact of western diet*** will further our knowledge of gene-environment interactions, provide the molecular evidence required for the prevention of chronic diseases through physical activity and healthy diet.
- We must identify those molecules that will allow early disease detection, and provide society with the information needed to counter the current strategy of increasing physical inactivity in our lives.
- Therefore, a fundamental question of biology is, how and why does the body adapt to physical inactivity?

Conclusion

- The Abundance of Food has becomes our worst Enemy and our biggest Weapon of Mass Destruction
- Majority of Death Today accounts for what we eat or not Ate
- Our comfort (Inactivity) has become death bed and slowly Journeying to Death
- Our Metabolic Functionality decrease 10% per each decade from the age of 30 (Short et al., 2003).
- Our Cell Oxidative capacity decrease as we age hence Most disease catches up with us with our bodies are less capacitated.

WAR III:
METABOLIC DISORDER BATTLE

- In Ancient times people died of Wars, Leprosies, infections
- World War I & II Led to Millions of losses in Life world wide
- World War III : METABOLIC DISORDER WAR (diseases emanating from these disorders)
- It is a battle within us
- If not suffering from it, you either have a family member or friend from Metabolic disorder/chronic diseases.
- It requires Weapons needing NO Nuclear armaments
- The use of Exercise & Diet to Survive/Adapt
- "If we don't end war, war will end us." - H. G. Wells
- "Mankind must put an end to war -- or war will put an end to mankind" (John F Kennedy).
- Chronic Diseases are killings millions of people, will they end man or man put an end to habits that promote these diseases?

Graduates in 2018

MSc

1. Bonolo Masilo
2. Mashudu Matumba
3. Victoria Fasiku
4. Brian Munansangu
5. Simon Isaiah
6. Mogorosi Masenye

PhDs

1. Dr Betty Ayeleso
2. Dr Shesan John Owonubi
3. Trevor Nyakunda [WITS]

POST DOC FELLOWS 2015-2018 IN NWU

1. Dr Sandile Fuku
(now Senior Lecturer in Biochemistry)
2. Dr Ademola Ayeleso
(now Senior Lecturer in Biochemistry)
3. Dr Amil Zohir
4. Dr Dr Tella Toluwani

Graduati on July 2018: MSc

PhDs
2018

GLORY BE GOD
WHO ALWAYS CAUSE TO
TRIUMPH THROUGH CHRIST
JESUS

2 CORITH 2:14

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- Ferrando AA, Paddon-Jones D, Wolfe RR. Bed rest and myopathies. Curr Opin Clin Nutr Metab Care 9: 410–415, 2006.

PUBLICATIONS

Some of the Publications Since Joining NWU in October 2014- June 2018

1. **Trevor T. Nyakudya, Pilani Nkomozepi, Emmanuel Mukwevho, Kennedy Erlwanger. (2018).** Neonatal intake of oleanolic acid attenuates the subsequent development of high fructose diet-induced non-alcoholic fatty liver disease in rats. ***Journal of Developmental Origins of Health and Disease*. In Press. DOI: 10.1017/S200174418259**

2. **Jitcy S. Joseph, Ademola O. Ayeleso, Emmanuel Mukwevho (2017).** Exercise increases hyper-acetylation of histones on the Cis-element of NRF-1 binding to the Mef2a promoter: Implications on type 2 diabetes. **Biochemical and Biophysical Research Communications, 22: 83–87.**

3. **Taiwo Betty Ayeleso, Mashudu Given Matumba and Emmanuel Mukwevho (2017).** Oleanolic Acid and Its Derivatives: Biological Activities and Therapeutic Potential in Chronic Diseases. **Molecules, 22, 1915-1931. doi:10.3390/molecules22111915**

4. **A Ayeleso, J Joseph, Y Belay, H Kinfe, S Mazibuko, O Oguntibeju, Emmanuel Mukwevho (2017).** Hybrid compounds from thiosemicarbazone and triazole as antidiabetic agents and their antioxidant potentials. **Biomedical Research 28 (1). 411-420.**

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