

Polycystic Ovarian Syndrome:

Definition and Epidemiology:

- Clinically: chronic anovulation with androgen excess
- Classic: anovulatory symptoms, polycystic ovaries, LH excess, ovarian hyperandrogenism
- Non-classic: variability in ovarian appearance, symptoms, and LH levels, ovarian and adrenal hyperandrogenism
- 5-10% of reproductive aged women

Pathophysiology:

Genetics:

- dominant inheritance; first degree relatives have PCO symptoms or early baldness

Insulin Resistance (IR):

- 95% have abnormal insulin signaling; a post-receptor defect
- Higher levels of insulin; initial compensatory hyperinsulinemia followed by beta cell failure and progression to NIDDM (especially in those with diabetic relatives)
- Weight loss improves resistance but doesn't improve beta cell defect
- ~40% decreased glucose uptake, similar to NIDDMs, independent of obesity
- Insulin induces ovarian androgen secretion, and potentiates LH's effect
- Insulin suppression reduces free testosterone levels and improves cycles

Secondary Implications:

Cardiovascular Disease:

- No definitive long term studies done
- IR raises CAD risk independently of other risk factors; indirectly raises VLDL causing a drop in HDL; directly stimulates atherogenesis on the vessel wall, reduced NO levels

Platelet Function:

- Increased platelet activation

Lipids:

- Impaired insulin dependent anti-lipolysis. Profile depends on BMI.
- Usually low HDL and high TG in obese women. In lean patients, normal levels, but HDL lower than age and weight matched controls

BP:

- Generally normal in early and young stages. Increases with age, three-fold higher risk later in life compared to age matched controls.
- Possibly due to decreased NO production due to IR

IGT and Type 2 Diabetes:

- IGT occurs in both lean (10.3%) and obese (40%) PCO women, vs. 10% IGT in general population
- Diabetes occurs in both lean (1.5%) & obese (5-10%) women with PCO.
- PCO women diagnosed by hyperandrogenism and anovulation almost always have IGT; but women defined by u/s findings don't always have it.
- Chronic anovulation as a symptom increases risk of DM
- Conversion from IGT to DM is 1-5%/year, up to 80% in 5 yrs if history of GDM

Obesity:

- 50-60% are obese.
- WHR is higher (up to 63% have > 0.8). 87.5% had BMI > 26
- High WHR is associated with higher risk of PCO, independent of BMI
- Android fat correlates with low HDL and high TG
- Cause of obesity not known, thought to be due to excess calorie intake.

Presentation:

1. Infertility- 40%
2. Infrequent or irregular periods (>35 days). 35% of amenorrheics, 73% of anovulatory women and 90% of oligomenorrheics have PCOS. Starts in adolescence; slow progression of symptoms. Rapid progression triggers suspicion. Patients often don't have symptoms of PMS, indicating no progesterone and anovulation.
3. Frontal alopecia, acne and oily skin.

Diagnosis:

Clinical:

1. Chronic oligomenorrhea
2. Clinical or biochemical hyperandrogenism
3. Rule out other causes: late CAH, hyperprolactinemia, androgenic tumors, Cushing's/acromegaly

On exam and lab:

- Signs of androgen excess: hirsutism, frontal alopecia (forehead and temples) and acne
- If virilization, suspect tumors
- Hyperinsulinemia may show acanthosis nigrans (brown thickening on elbows & knees)
- WHR, central obesity
- Variable lab findings (during follicular phase): overall LH increased (except in obese), DHEAS and free TT increased, reduced SHBG and FSH
- OGTT more useful than fasting glucose or HbA1C
- Fasting insulin may be useful (levels correlate with degree of IR, but not standardized)
- HDL, LDL, TG recommended
- If suspicious: rule out other conditions with appropriate bloodwork

Management:

Diet and Exercise:

- First line management.
- Lowers insulin levels to normal. Uncertain how much needed 2-5%(?)
- May reduce TC (15%), raise HDL (10%), small study.
- Variable effect on hormones, generally: raise SHBG, reduce total TT and free TT (not always), and lower LH
- Return to normal periods (80%), documented ovulation only 33%
- Calorie reduction necessary; no difference in RMR or thermogenesis.
- Exact diet composition not known, but since beta defect present in subset, low GI diet may be helpful
- Increasing dietary fiber known to be inversely related to insulin levels

Pharmacologic:

IGT:

- Metformin reduces TG, LDL and BP in some studies.
- Variable effect; some suggest all related to weight loss independent of Metformin
- Thiazolidinediones: reduce IR, improves lipids and insulin levels
- Studies show hyperinsulinemia and androgenism improved.
- Not considered first line therapy yet.

Menstruation and Fertility:

- Endometrial protection: Induce periods if fewer than 4/year.
- If need contraception, use BCP with low estrogen. If not needed, use Provera 5-10 mg/d for 10-14 days/month.
- Must always rule out pregnancy first since treatment can induce abortion
- Infertility: weight loss of 5% results in 70% spontaneous conception and 40% less hirsutism
- If unsuccessful or unwilling, use clomiphene or send to gyne/fertility specialist

Androgen Excess:

- Hair follicle can't resort to normal, cosmetics needed and takes up to 5 months
- First line is weight loss (5-10%) improves signs.
- Second line: BCP (Diane 35)
- Third line: anti androgen (contraindicated in pregnancy), spironolactone, either alone or in combination (even more effective) 50 mg bid.
- Finasteride may have less S/E's but not more effective.
- Frontal alopecia: anti androgen, but results not very successful.

Role of Dietary Fat in General Health.

Saturated fatty acids:

These fats do not have any double bonds, therefore called saturated. They are most commonly found in tropical oils, animal fats and foods made with tropical oils. The most common are: palmitic, stearic, myristic and lauric. Increased consumption of saturated fatty acids can increase LDL cholesterol in some patients. Patients that do not have an increase in LDL have an increased expression of LDL receptors, therefore maintaining their LDL level. The other individuals cannot up-regulate LDL receptor production and therefore have an increased LDL level. The greatest increase in LDL occurs with myristic, next palmitic then lauric. Stearic acid (found in chocolate) does not increase LDL since it is rapidly converted to oleic acid, which is a monounsaturated fat.

Transfatty acids:

Normally fatty acids occur in the “cis” isomer, in which the hydrogens are on the same side of the carbons. In the transfatty acids, the hydrogen atoms are on the opposite side of the carbon atoms. These are usually produced in response to hydrogenating or partially hydrogenating monounsaturated fatty acids. They are most prevalent in baked products, snacks, fast foods and food cooked in restaurants using these oils. Partially hydrogenating these oils allows production of semisolid and more stable fats. The transfatty acids increase LDL and reduce HDL, therefore having a significant increase in the Total Cholesterol/HDL ratio. This increase exceeds the increase found with saturated fats. It has also been found to increase fasting lipoprotein (a) and triglyceride.

To calculate transfatty acid, subtract SFA, PUFA and MUFA from the total fat content. One form of TFA, conjugated linoleic acid, found in dairy products has been shown to have some beneficial health properties. In the nurse’s health study, TFA’s were found to increase the risk of CAD. Some patients use CLA for weight loss (Tonalin) but research is not conclusive. Some animal models have shown it to be of benefit. Other research has suggested while it may contribute to weight loss, there is a possibility of lean muscle loss. Another area of interest with CLA is the potential of its role in malignancy. Studies suggest that it is cytotoxic to melanoma, colorectal and breast cancer cells in vitro.

MUFA's:

Monounsaturated fatty acids have one double bond. They are found in olives, canola, many nuts and avocado. The most common form is oleic acid, which is an omega-9 fat. Oleic acid can be made by conversion of stearic acid. In the 1970s, Keys’ study showed a relationship between a Mediterranean diet and a lower risk of coronary artery disease. This diet included increased intake of fruits and vegetables and MUFA's. MUFA's reduced total and LDL cholesterol compared with SFA's. Studies show that compared to a high carbohydrate diet, increasing MUFA's reduces triglyceride and increases HDL levels. In addition, compared to a high carbohydrate diet, MUFA's improve insulin sensitivity and improve glycemic control in

Type II diabetics. This accounts for the recent recommendation of increasing MUFA's in diabetic patients. MUFA's also appear to reduce the susceptibility of LDL to be oxidized.

PUFA's:

Polyunsaturated fatty acids are divided into omega-3 and omega-6. The number refers to the location of the double bonds from the terminal carbon end.

Omega-6 to have their double bonds at the sixth carbon from the end. The most important is linoleic acid, which is considered an essential fatty acid since it cannot be produced by the body and must be ingested. It is available in seeds and vegetables and nuts. It has been shown that if you replace SFA's with omega-6 you reduce total and LDL cholesterol. Some studies have shown a concomitant reduction in HDL but this is not consistent.

There are three main Omega-3 fats: ALA (alpha-linolenic acid, 18:3) found in flax, canola, walnuts and soy. EPA (eicosapentoic acid, 20:5) and DHA (docosahexenoic acid, 22: 6). Both EPA and DHA are found in fatty fish.

Fat	Source	Name	LDL Effect	HDL Effect	TG Effect
Saturated	Tropical Oils, animal products,	Palmitic	↑↑	↑	Nil
		Stearic	Nil	↑	Nil
	butter, cheese	Myristic	↑↑↑	↑	Nil
		Lauric	↑	↑	Nil
Trans Fat	Hydrogenated Oils	Elaidic Acid	↑	↓	Nil
Monounsaturated	Olives, Avocado	Oleic	↓	↑	↓ or nil
Omega 3 Polyunsaturated	Flax, Canola, green leafy vegetables	Alpha-Linolenic Acid (ALA)	↓	?	↓
	Fish Oils	Docosahexenoic Acid (DHA) Eicosapentoic Acid (EPA)	↓ or ↑	?	↓
Omega-6 Polyunsaturated	Vegetable Oils	Linoleic Acid	↓	↓↑ or nil	↓

Role of Omega-3's & 6's

A great deal of interest has been targeted towards the role of omega-3 fats in chronic disease. Omega-3's lower cholesterol and triglyceride by reducing VLDL synthesis. This appears to be a feature of EPA and DHA and not seen with plant omega-3's. They also promote the metabolism of VLDL, reduce apo-lipoprotein B and LDL synthesis and also reduce post-prandial lipemia. If saturated fatty acid is replaced with omega-3 fats, LDL levels dropped, but if omega-3's are added to SFA's then there is no change in LDL or a possible increase occurs. A very interesting finding has been that they stimulate endothelial derived nitric oxide production.

On the next page you will see the metabolism of Omega 3 and 6 fatty acids and the role they play in the inflammatory cascade.

Omega 3 Fatty Acids

ALA -Alpha Linolenic Acid (found in flax seed, hemp, canola, walnuts)

↓

via delta 6 desaturase enzyme (a rate limiting step)

↓

SA-Stearidonic Acid (in black currant seed)

↓

EA-Eicosatetraenoic Acid

↓

via delta 5 desaturase enzyme (a rate limiting step)

↓

EPA-Eicosapentaenoic Acid

(found in fish, inhibits Arachidonic Acid cascade, by reducing desaturase activity, reduces clotting)

EPA→ Series 3 PGs (PGE₃, PGH₃, PGI₃,TXB₃) which are anti-inflammatory

↓

via delta 4 desaturase enzyme

↓

DHA-Docosahexanoic Acid (brain and eye development, ?depression, ?BAD, ?ADD, ?AD)

Omega 6 Fatty Acids

LA-Linoleic Acid (sunflower, safflower, corn oil)

↓

via delta 6 desaturase (a rate limiting step)

↓

GLA-Gamma Linoleic acid (in borage and primrose oil)

↓

DGLA-Dihomogammalinoleic Acid (breast milk) → via delta 5 desaturase → **AA**- Arachidonic Acid

↓

↓via lipoxygenase 15

via COX

15HETrE (turns off Lipoxygenase 5, reducing AA LT metabolites)

↓

Series 1 PGs (vasodilatation, ↓ platelet aggregation, ↓ arterial BP, ↓ thrombus, ↓ inflammation)

AA → via COX (↓ by ASA) → Series 2 PGs (PGE₂, TXA₂ etc-↑ inflammation/pain/vasoconstriction)

↓

via Lipoxygenase 5

↓

LT A-E₄ (asthma mediators)

To understand better we need to look at eicosanoid production. Eicosanoid is the collective term to include thromboxanes, prostaglandins and leukotrienes. On the previous page is a schematic of omega-3 and Omega-6 metabolism, leading to eicosanoid production. Eicosanoids are produced along both lines, omega-3 and Omega-6.

Phospholipase enzyme releases arachidonic acid from cell membranes and makes it available for metabolism either along the cyclo-oxygenase pathway (to produce PG and TX) or lipoxygenase pathway (producing LT). Anti-inflammatory medications block the COX enzyme and therefore reduce thromboxanes and prostaglandins synthesis, and have no effect on leukotrienes whereas steroids block of the action of phospholipase and therefore reduce thromboxanes, leukotrienes, and prostaglandins production. Hence the reason we do not prescribe anti-inflammatory medications to reduce asthma symptoms. It is postulated that asthmatic ASA sensitivity is due to the fact that blocking COX by ASA leads to more buildup of AA with only the lipoxygenase pathway open...leading to increased LT's and subsequent asthma symptoms.

Mammals cannot interconvert omega-3 and Omega-6 fat. Both paths use Delta 6 and Delta 5 desaturase enzymes. Therefore there is a competition between paths and if a diet is too high in Omega-6 fats relative to the omega 3, there is an increased production of pro inflammatory leukotrienes, thromboxanes and prostaglandins compared with the less biologically active prostaglandins derived from EPA. A diet rich in LA reduces ALA conversion by 40 percent. A high maternal consumption of LA reduces EPA and DHA levels in umbilical plasma. SFA's and TFA's also reduce ALA desaturation to EPA and DHA.

While the proper ratio of Omega-6 to omega-3 fats is unknown, some suggest that the Paleolithic diet range from a 1: 1 to 4: 1 ratio respectively. Current North American consumption is closer to 25 or 30:1 in favour of the omega-6.

Trial Results

So, the question is what do the trials say about the omega-3 fats?

Some of the more recent studies include the Mr. FIT, health professionals' follow-up study, Lyon diet heart study, the nurse's health study and the DART study.

The Mr. FIT study was a primary prevention trial involving 12866 men between the age of 35 - 57. In it, intake of omega-3 fats (ALA and fish) was inversely associated with mortality from coronary artery disease, cardiovascular disease and all causes. There was also an inverse relationship with stroke risk.

The health professionals' follow-up study began in 1986 and was a large-scale prospective cohort study. They found in an age-adjusted analysis of dietary fat intake and risk of myocardial infarction, ALA as a percent of total energy was inversely associated with risk of MI and fatal coronary disease. There was no association between increasing fish intake and

coronary disease. The authors concluded that increasing fish more than one to two servings per week were unlikely to improve primary prevention of coronary artery disease.

In the Lyon diet heart study, patients who had had a previous MI were recommended a Mediterranean type diet rich in ALA. Although there was not a significant reduction in cholesterol and triglyceride, there was a 50 to 70 percent reduction in cardiac end points as defined by cardiac death and nonfatal MI, unstable angina, stroke, congestive heart failure, pulmonary embolus or hospitalization.

It was questioned whether the reduction was due to the antithrombotic or anti arrhythmic effects of omega-3 fats. ALA, not EPA or DHA was significantly associated with protection of MI recurrence. Other studies have shown that EPA and DHA exert this benefit also. The study was followed up and shown to be beneficial up to four years after initial randomization. It also showed that most patients still followed the Mediterranean diet recommendation long after being randomized to the study. The authors therefore conclude that you can exert long-term behavioural change with patients.

The nurse's health study began in 1976 with more than 76, 000 participants. It showed that the highest quintile of ALA consumption had lower relative risk of fatal and nonfatal infarction.

Another study, in JAMA in 1995, quantified the risk reduction and suggested that compared to not eating seafood, eating fatty fish twice per month is associated with a 30 percent reduction in risk of primary cardiac arrest. Consuming one fatty-fish meal per week is associated with a 50 percent reduction in risk of primary cardiac arrest.

The DART study included men who had recovered from infarction and were advised to eat fish twice per week. These men had a 29 percent reduction in two-year all cause mortality versus those who were not advised the fish weekly. The study did not record arrhythmic deaths. This reduction was observed even though there was no significant change in cholesterol and very few participants took aspirin.

In the physicians' health study, which was a prospective cohort study, omega-3 from seafood was associated with a decrease in risk of sudden death but there was no association between fish oil and incidence of infarction. As some suggest, omega-3 fats may not reduce the risk of having an infarct but make them less deadly.

A recent study presented at the American Heart Association annual meeting showed a reduced risk of dying from infarction, and an increase plasma DHA and EPA level with consuming fish. This change is seen especially in the two weeks prior to consuming fish. The study went on for almost seven years and recorded deaths from infarction and nonfatal infarcts. Consuming fish once per week showed a 35 percent reduction in risk of death from ischemic heart disease, but did not reduce the risk of nonfatal infarcts.

Regarding blood pressure: a study in 1999 showed groups given MUFA's and PUFA's had lower mean arterial pressure than patients consuming SFA's. It is not clear whether this change is sustainable over the long-term.

The GISSI Prevenzione trial included more than 11,000 patients less than three months post infarction. There was a 42-month follow-up and patients were randomized to EPA and DHA supplementation with or without vitamin E. Some patients were also using aspirin, beta-blockers or ACE inhibitors. The study was associated with a 20 percent reduction in overall mortality in patients using the omega-3 supplementation and a 45 percent reduction in sudden death.

While some of the basic biochemistry is compelling, we're not certain exactly how PUFA's exert their effect. Some thoughts include:

1. Increasing omega 3 fats in the diet increases the ALA contents of cell membranes. It is thought that this stabilizes electrical activity possibly by its effect on ion exchange channels. This is felt to be the reason that death rates are lower post MI: membrane omega 3 fats appear to be anti arrhythmic.
2. ALA competes with LA for Delta 6 desaturase enzymes. If there is sufficient ALA, this is converted into EPA, if conversion is insufficient; one needs the EPA through their diet. EPA reduces AA metabolism into proinflammatory PG's.
3. With respect to atherosclerosis: we are now seeing a strongly inflammatory component to the development of atherosclerosis. The questions exist as to the usefulness of omega-3 and 6 fats to reduce the progression of atherosclerosis based on their anti-inflammatory effects.
4. Fish oil prolongs bleeding time and this effect is additive to ASA.

The role of omega-3 and 6 fats in immune function:

ALA has been shown to suppress proliferation of mononuclear lymphocytes in peripheral blood. It also suppresses the delayed hypersensitivity reaction to some antigens.

Increased levels of the ALA in membranes phospholipids results in a reduced production of arachidonic acid from LA, and reduced synthesis of pro inflammatory eicosanoids leukotriene B₄ and thromboxane A₂. Prostaglandin I₃, derived from EPA, appears to be less inflammatory. One study showed total prostaglandin reduction of 50 percent by increasing ALA to 8 percent of total caloric energy intake.

Some studies are suggesting the role for omega-3 fats in autoimmune disease modulation. ALA and the ALA: LA ratio affects production of tumor necrosis factor (TNF) and interleukin 1 (IL-1) by macrophages.

TNF and interleukin 1 stimulates the release of platelet activating factor, which is a mediator of inflammation.

Unfortunately we do not know which is the more effective of the omega-3 fats. ALA is primarily found in flax and vegetable sources while DHA EPA are found fish.

Patients with RA and active synovitis were given GLA (between 1.4g – 2.8 g per day) for one year. The patients that were using the GLA for the whole year had a progressive improvement in symptoms. GLA bypasses the rate limiting step of delta 6 desaturase, therefore increasing DGLA levels, which contribute to the anti inflammatory PG's.

Flax as a source of Omega-3's

Let's discuss flax specifically for a couple of minutes. In patients with systemic lupus (SLE) there is an increased production of platelet activating factor. One study of 9 patients with lupus nephritis showed a reduction in platelet activating factor and an improvement in renal function with increasing omega-3 in the form of flax. It is not certain why, but some believe this effect to be related to lignans found in the flax.

Lignans are phytoestrogen phytochemicals with a possible anticancer, anti-inflammatory and anti-mitotic activity. You may have heard of a recent study released in the media that found ground flax reduced the progression of breast cancer. Some believe this may be related to its phytoestrogen properties.

A new lignan, cinnamophilin, has been shown to reduce thromboxane synthase therefore reducing thromboxane A2 production. Lignans are found in unrefined grains, barley, millet, oats, soybeans and some vegetables such as broccoli, cauliflower, spinach and carrots.

So, does flax reduce tumors in human beings? Possibly.

1. Lignans appear to be most effective for hormonal tumors. Some studies show lignans stimulates liver synthesis of sex hormone binding globulin therefore reducing circulating estrogens. They have also been shown to bind to estrogen receptors on sex hormone binding globulin therefore reducing estrogen and testosterone binding and possibly interfering with estrogen mediated tumor production.
2. Lignans have been shown to suppress differentiation and growth of cultured human leukemic cells.
3. Populations with high intake of phytoestrogens have lower incidence of breast, prostate and endometrial cancer.

Where to go from here: Recommendations from Health Organizations

Health Canada recommends at least 0.5 percent of total energy intake to come from omega-3 fatty acids and approximately three percent of total energy intake to come from linoleic acid. For the average 2000-calorie diet this would equal approximately one gram of omega-3 fats per day. One tablespoon of whole flaxseed gives 2.5 g of ALA. Clinically, to avoid deficiency, one only requires 1 to 2 percent of total energy to come from LA, and it is estimated that Omega 3 of the requirement is 25 percent that of Omega-6.

While it is not known the exact amount of omega-3 that we should be consuming, it is suspected that 1 g of ALA and 300-400 milligrams of EPA and DHA is required for children and adults. One must keep in mind that in pregnant women, omega-3 fat is transferred across the placenta and DHA is incorporated into the brain and retina of the developing fetus. Therefore during pregnancy, omega-3 intake should be increased. It has been shown that premature infants given formula that has been fortified in DHA develop visual acuity faster than preemies given regular formula.

There is no evidence to date that fish oil supplementation prevents coronary artery disease.

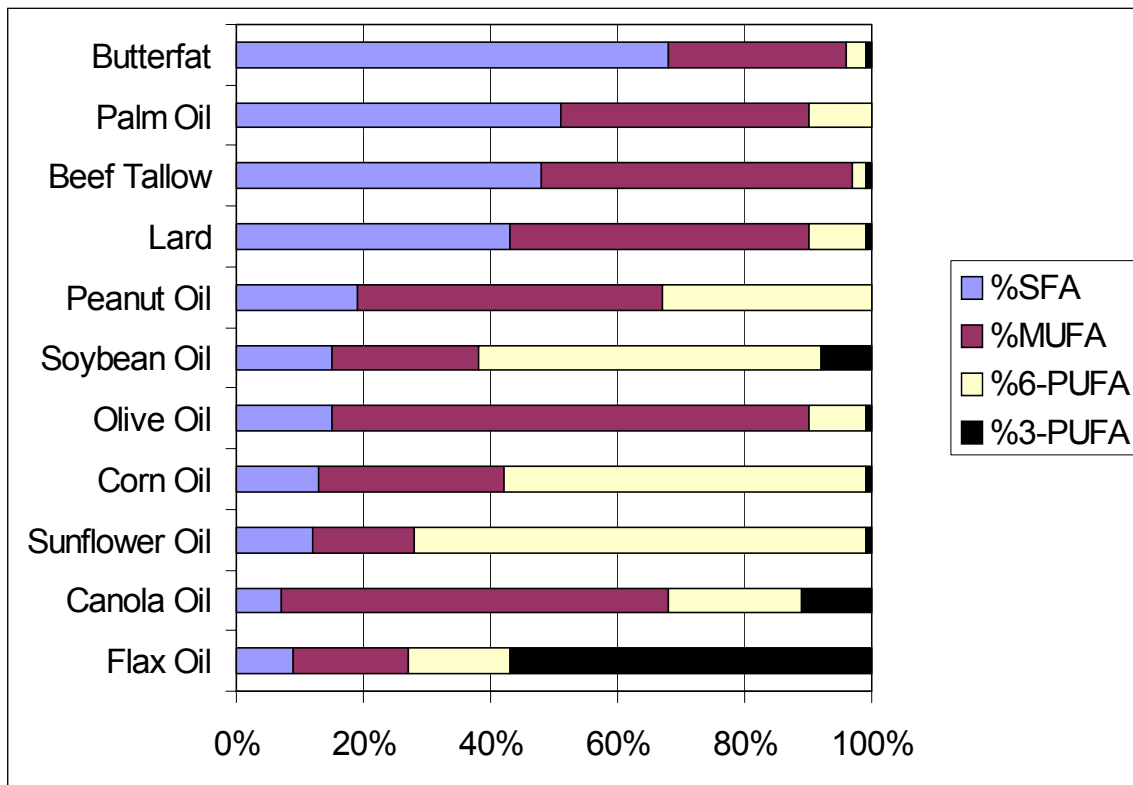
The American Heart Association recently revised their guidelines in October 2000.

Some of the recommendations include:

1. Reduce SFA and TFA intake. Substitute SFA's with MUFA's, PUFA's and fiber. SFA and TFA total should be less than 10 percent of total calorie intake per day.
2. There is no evidence that increasing HDL by diet reduces coronary artery disease risk. Therefore it is more important to increase HDL by decreasing body fat and increasing activity. It has been noted that low-fat, high carbohydrate diets can reduce HDL levels in some patients.
3. Patients with low HDL and high triglyceride should reduce weight, increase activity and reduce carbohydrate intake.
4. Some patients are more sensitive to cholesterol intake. In general individuals should reduce their cholesterol intake. A recent study showed that one egg per day did not have any deleterious effects on lipids.
5. At least two servings of fatty fish per week (12 oz) are recommended.
6. "In the absence of weight loss, diets high in total carbohydrate (greater than 60 percent) can lead to elevated triglyceride and reduce HDL". Diets rich in unsaturated fatty acids vs. carbohydrate may help modulate atherogenic dyslipidemias.
7. In Type II diabetes, individuals should reduce SFA's to less than 7 percent of total daily caloric intake. Cholesterol intake should be less than 200 milligrams per day. Low glycemic index carbohydrates have been shown to improve glucose levels, but there are concerns about the practicality and implementation in real life. Type II diabetics should also increase MUFA's especially to replace SFA's.

Fatty Acid Composition of Common Dietary Fats

	%SFA	%MUFA	%6-PUFA	%3-PUFA
Flax Oil	9	18	16	57
Canola Oil	7	61	21	11
Sunflower Oil	12	16	71	1
Corn Oil	13	29	57	1
Olive Oil	15	75	9	1
Soybean Oil	15	23	54	8
Peanut Oil	19	48	33	tr
Lard	43	47	9	1
Beef Tallow	48	49	2	1
Palm Oil	51	39	10	Tr
Butterfat	68	28	3	1



Eicosanoid	Major site(s) of synthesis	Major biological activities
PGD ₂	mast cells	inhibits platelet and leukocyte aggregation, decreases T-cell proliferation and lymphocyte migration and secretion of IL-1a and IL-2; induces vasodilation and production of cAMP, mast cell activation
PGE ₂	kidney, spleen, heart	increases vasodilation and cAMP production, enhancement of the effects of bradykinin and histamine, induction of uterine contractions and of platelet aggregation, maintaining the open passageway of the fetal ductus arteriosus; decreases T-cell proliferation and lymphocyte migration and secretion of IL-1a and IL-2, increase vascular permeability, diuresis, erythema, fever, renin release, reduction of gastric acid secretion, stimulation of gastric mucus and fluid secretion and duodenal HCO ₃ secretion, inhibits LTB ₄
PGF _{2a}	kidney, spleen, heart	increases vasoconstriction, bronchoconstriction and smooth muscle contraction, fever
PGH ₂		precursor to thromboxanes A ₂ and B ₂ , induction of platelet aggregation and vasoconstriction
Prostacyclin or PGI ₂	heart, vascular endothelial cells	inhibits platelet and leukocyte aggregation, decreases T-cell proliferation and lymphocyte migration and secretion of IL-1a and IL-2; induces vasodilation and production of cAMP, fever
TXA ₂	platelets	induces platelet aggregation, vasoconstriction, lymphocyte proliferation and bronchoconstriction
TXB ₂	platelets	induces vasoconstriction
LTB ₄	monocytes, basophils, neutrophils, eosinophils, mast cells, epithelial cells	induces leukocyte chemotaxis and aggregation, vascular permeability, T-cell proliferation and secretion of INF-g, IL-1 and IL-2
LTC ₄	monocytes and alveolar macrophages, basophils, eosinophils, mast cells, epithelial cells	component of SRS-A, induces vasodilation, vascular permeability and bronchoconstriction and secretion of INF-g
LTD ₄	monocytes and alveolar macrophages, eosinophils, mast cells, epithelial cells	predominant component of SRS-A, induces vasodilation, vascular permeability and bronchoconstriction and secretion of INF-g
LTE ₄	mast cells and basophils	component of SRS-A, induces vasodilation and bronchoconstriction

Vitamin D:

One of the 4 essential fat soluble vitamins

Produced in the body under the influence of Ultraviolet B light from the sun

Not available even in breast milk

Responsible for many things including: calcium absorption, bone strength, immune function, cancer prevention (especially prostate), some question whether it has a role in multiple sclerosis and mood disturbance.

Uncertain what the minimum daily requirement is. Used to be 400 IU per day, now being suggested to have 800-1000 IU per day.

Deficiency leads to rickets, which disappeared years ago when parents used to give their children cod liver oil. A recent rise in rickets in children has been linked to dietary deficiency.

Countries that have high fish consumption and sunlight have low levels of prostate cancer and MS.

The sun is not strong enough between the months of October and March to produce Vitamin D in the body; therefore it is a good idea to take a supplement during the fall and winter months; all year if you avoid the sun.