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Polygenic Primary Hypertriglyceridemia: Mechanisms, Phenotypes, and Management

Mechanisms and Pathophysiology

Polygenic **primary hypertriglyceridemia (HTG)** arises from the combined effect of multiple genetic variants that disrupt triglyceride metabolism. Unlike rare monogenic forms (e.g. familial chylomicronemia due to homozygous *LPL* mutations), polygenic HTG involves heterozygous variants in key triglyceride pathways plus a burden of common polymorphisms [1]. The result is a milder but variable phenotype, heavily modulated by lifestyle factors [2]. Fundamentally, HTG can develop from **excess production** of triglyceride-rich lipoproteins or **impaired clearance** (or both) [3]. In polygenic HTG, both mechanisms often contribute: the liver may overproduce very-low-density lipoproteins (VLDL) carrying triglycerides, and peripheral clearance of chylomicrons/VLDL is moderately inefficient due to partial enzyme or apolipoprotein defects [3].

Hepatic VLDL overproduction: Many individuals with polygenic HTG have underlying insulin resistance (as in metabolic syndrome), which increases the flux of free fatty acids to the liver and upregulates VLDL secretion. Genetic variants can exacerbate this. For example, loss-of-function mutations in the APOC3 gene (encoding apolipoprotein C-III) are associated with low triglycerides, whereas common promoter variants that raise apoC-III levels lead to higher triglycerides [4] [5]. ApoC-III is a key regulator that **inhibits lipoprotein lipase (LPL)**, **blocks hepatic uptake of triglyceride-rich remnants**, and **enhances VLDL assembly/secretion** [4]. Elevated apoC-III (often >30 mg/dL in HTG patients, vs. normal ~7–12 mg/dL) thus promotes triglyceride accumulation [5]. High carbohydrate diets can further aggravate this: glucose intake activates the carbohydrate-responsive element binding protein (ChREBP) in the liver, which increases *APOC3* transcription and in turn raises VLDL-TG levels (one study showed a ~2-fold increase in fasting TG with high glucose intake via this mechanism) [6] [7]. In short, genetic predisposition coupled with diets rich in sugars/refined carbs can drive hepatic **overproduction of VLDL triglycerides**. Excess alcohol intake is another potent trigger for VLDL overproduction, as alcohol increases hepatic fatty acid synthesis; this is why alcohol often precipitates very high TG in susceptible individuals (a moderate alcohol load can acutely raise plasma TG by ~50% above baseline within hours) [8].

Impaired lipolytic clearance: Triglyceride-rich lipoproteins (chylomicrons from the gut and VLDL from the liver) are normally cleared by LPL, which hydrolyzes TG at the capillary endothelium. Polygenic HTG frequently involves partial defects in this clearance pathway. Common or heterozygous variants in the "canonical" TG metabolism genes – *LPL* itself, its cofactor *APOC2* (apo C-II), *APOA5* (apo A-V), *GPIHBP1*, and *LMF1* – can modestly reduce the efficiency of LPL-mediated lipolysis [9]. For instance, apo C-II is required to activate LPL; if apo C-II is slightly deficient, LPL activity falls. Apo A-V normally helps tether TG-rich particles to LPL and cell surfaces (stabilizing the LPL–lipoprotein complex), so APOA5 variants can lead to higher TG – animal models show apoA-V knockout quadruples TG levels [10] [11]. Conversely, overexpressing apoA-V drastically lowers TG [12]. On the other hand, **apo C-III** (discussed above) and the angiopoietin-like proteins **ANGPTL3/4** act as natural LPL inhibitors; high levels of these proteins slow down TG clearance [13] [14]. Indeed, experimental overexpression of human apoC-III in animals triggers severe HTG, underscoring its

role in pathophysiology [15]. Many polygenic HTG patients have a combination of common risk alleles – for example, a mildly deleterious LPL variant plus an apoA5 variant plus a promoter that raises ANGPTL4 – which together lead to a meaningful decrease in triglyceride clearance. The end result is an accumulation of VLDL and remnant lipoproteins in plasma [16] [3]. Notably, **mild-to-moderate HTG** (triglycerides in the 150–500+ mg/dL range) mainly reflects high VLDL and remnants, whereas **severe HTG** (often >1000 mg/dL) indicates chylomicrons appearing even in fasting blood (a sign that clearance is extremely impaired) plus excess VLDL [16]. Polygenic HTG can span this spectrum depending on secondary factors.

In summary, polygenic primary HTG is a multifactorial condition in which **multiple small-effect genetic variants** in TG metabolic pathways (lipoprotein lipase and its regulators, apolipoproteins like C-II, C-III, A-V, and others) collectively cause a **"traffic jam" of triglycerides** – too many TG-rich particles produced by the liver, and not cleared quickly enough in the circulation [3]. This contrasts with monogenic HTG (familial chylomicronemia syndrome), where a single crucial gene is knocked out and causes extreme HTG regardless of environment [9] [1]. In polygenic HTG, the genetic burden is more subtle and the phenotype **"takes a village"** of genetic hits plus environmental triggers. Importantly, the **pathophysiology is greatly modulated by lifestyle** – factors like diet composition, body weight, alcohol use, and insulin sensitivity can tip the balance between moderate and severe HTG [17]. For example, one person might carry several TG-raising gene variants yet have only mild triglyceride elevation if they are lean and active, whereas the same genetic makeup in an individual who is obese and consuming excess sugars or alcohol may result in dramatically higher TG levels due to synergistic overproduction and impaired clearance.

Typical Phenotypes and Clinical Characteristics

Prevalence and demographics: Polygenic hypertriglyceridemia is common in the general population. By standard criteria, about *10% of adults worldwide* have elevated fasting triglycerides (HTG) above ~150 mg/dL [18], though definitions vary. In the United States, a more sedentary and high-calorie environment has led to even higher prevalence – one large survey found **33% of U.S. adults** have TG ≥150 mg/dL, about 18% have TG ≥200 mg/dL, and ~1.7–2% have *severely* elevated levels ≥500 mg/dL [19]. Truly extreme triglyceride levels (≥1000 mg/dL) are relatively rare (on the order of 0.4% of individuals) [20], usually arising only when genetic predisposition and secondary factors coincide. There is considerable inter-ethnic and regional variability, attributable to differences in diet and genetic backgrounds [18]. For instance, populations with higher rates of metabolic syndrome (such as some South Asian and Hispanic groups) tend to have more HTG, whereas certain African populations have lower TG on average despite obesity (possibly due to genetic lipid profiles). **Age and sex** also influence the phenotype: triglycerides tend to rise with age and post-menopausal status. Men often have higher TG in young adulthood, but women catch up after menopause (due to loss of estrogen's TG-lowering effect). Familial clustering of moderate HTG is common – polygenic HTG often manifests in multiple family members, though not necessarily in a Mendelian pattern [21].

Phenotypic variation: A hallmark of polygenic HTG is its *wide phenotypic heterogeneity*. Baseline triglyceride levels can range from just above normal (e.g. 150–200 mg/dL) to many thousands in extreme cases, depending on lifestyle and co-morbid factors [2]. In fact, the same individual's TG levels may fluctuate dramatically under different conditions. Commonly, people with polygenic HTG have **mild-to-moderate elevations** (say 200–600 mg/dL) when following a healthy lifestyle, often with no symptoms. They may be identified incidentally on routine bloodwork. These individuals are frequently **asymptomatic**; apart from the laboratory finding of high TG, they might have nothing remarkable, and total cholesterol can be near-normal (polygenic HTG of the "familial type IV" pattern often features triglycerides 200–1000 mg/dL with normal or only slightly elevated cholesterol) [21]. Importantly, **environmental and behavioral factors**

profoundly impact the TG level in polygenic HTG. For example, a **lean, physically active person** with a given genetic makeup might maintain fasting TG around 150–250 mg/dL, whereas an **overweight, sedentary relative** with the same genes could run TG in the many hundreds [21]. Diet plays a major role: a high-carbohydrate diet or regular intake of sugary drinks can exacerbate VLDL production and raise TG significantly, while a low-carb or balanced diet can keep levels in check. **Alcohol consumption** is a notorious amplifier of polygenic HTG – it's not uncommon for patients who habitually consume excessive alcohol to present with TG levels in the 1000–2000+ mg/dL range, whereas if they abstain, their levels might fall to a few hundred. In one study, patients with baseline hypertriglyceridemia saw fasting TG shoot up to ~358 mg/dL after moderate alcohol, versus ~89 mg/dL in those without predisposition [22]. Clinically, we often see that **secondary factors "unmask" the genetic tendency**: as an expert put it, primary HTG may not reveal itself without a secondary "insult" – e.g. a patient with a mild genetic load might only spike >300 mg/dL after gaining weight or starting to drink regularly [23] [24]. Indeed, a **secondary component** such as *alcohol use or a high-carbohydrate diet* is commonly noted in those with familial (polygenic) HTG [21]. Conversely, weight loss, exercise, and low-sugar diets can dramatically reduce TG in these individuals (often normalizing the levels). Thus, polygenic HTG spans a continuum: at one end, a fit individual may just have borderline-high TG; at the other, the combination of genetic susceptibility with obesity, diabetes, and alcohol can lead to what's sometimes called **"multifactorial chylomicronemia syndrome,"** an extreme HTG state resembling familial chylomicronemia [25].

Lipid profile and co-abnormalities: In polygenic HTG, the **triglyceride elevation often comes with low HDL cholesterol** ("good cholesterol") and a preponderance of small dense LDL particles – especially in patients with insulin resistance. This trio (high TG, low HDL, small LDL) is the classic dyslipidemia of metabolic syndrome and is considered pro-atherogenic. However, there are subtypes; some individuals with familial HTG (type IV) have isolated high VLDL but relatively normal LDL and HDL levels – these cases have been historically thought to have **lower cardiovascular risk** than mixed dyslipidemias [21]. By contrast, **familial combined hyperlipidemia** (another polygenic disorder) features elevated TG *and* elevated LDL, conferring high atherosclerotic risk. Pure chylomicronemia (monogenic) interestingly does *not* raise LDL or cause plaque buildup (chylomicrons are too large to penetrate the arterial wall) [26]. Most polygenic HTG patients fall in between: they have elevated VLDL and remnants, which do carry cholesterol and can contribute to arterial plaque. Modern evidence indicates that **remnant lipoproteins** (the TG-rich remnants of VLDL and chylomicrons) are highly atherogenic [27]. Thus, even moderate HTG is associated with increased risk of cardiovascular disease. In fact, hypertriglyceridemia is linked to higher incidence of coronary artery disease (especially when accompanied by low HDL) [28]. Many such patients also have **non-alcoholic fatty liver disease (NAFLD)**, as triglyceride-rich VLDL production goes hand-in-hand with fat deposition in the liver [27]. NAFLD is commonly seen in those with polygenic HTG and metabolic syndrome.

Associated pathologies: The two major clinical complications of HTG are **pancreatitis** and **atherosclerotic cardiovascular disease**. The risk of **acute pancreatitis** rises exponentially with triglyceride levels. Typically TG > 500 mg/dL is considered a threshold where pancreatitis risk becomes significant, and at **levels >1000 mg/dL the risk is substantial (~5% or more)** [29]. If TG climbs to extremely high concentrations (e.g. >2000–>3000 mg/dL), pancreatitis risk may reach 10–20% or higher [29]. Clinically, patients with polygenic HTG can develop pancreatitis if a secondary trigger causes an acute TG spike – for example, an **alcohol binge or uncontrolled diabetes** could send TG from 600 to 2000 mg/dL and precipitate pancreatitis. In individuals with chronic HTG in the 1000+ range, up to ~10% will experience pancreatitis over time [30]. Therefore, prevention of pancreatitis is a primary concern in those with very high TG. On the other hand, the relationship between **triglycerides and atherosclerosis** has been historically debated, but it is now recognized that elevated TG (especially in the form of cholesterol-rich remnant particles) correlates with

higher risk of coronary disease [28]. Large epidemiologic studies have shown that even moderately high TG (200–500 mg/dL) is independently associated with cardiovascular events, although the risk is partly mediated by accompanying low HDL and metabolic factors. Polygenic HTG patients who also have **familial combined hyperlipidemia or metabolic syndrome** are at particularly elevated cardiovascular risk, whereas those with isolated HTG (normal LDL) may have a more modest risk increase [21]. In summary, a **mild-to-moderate HTG phenotype** often signals underlying metabolic issues that predispose to heart disease (and indeed HTG is linked with conditions like insulin resistance, inflammation, and visceral adiposity), while a **severe HTG phenotype** (>1000) carries the acute danger of pancreatitis in addition to any chronic cardiac risk [27]. Other associated conditions include eruptive xanthomas (yellowish papules on skin when TG is extremely high), lipemia retinalis (milky appearance of retinal vessels), and hepatosplenomegaly – these occur mainly in severe cases with chylomicronemia. Most patients with polygenic HTG will *not* have these extreme signs, but milder features like **fatty liver** and **metabolic syndrome** (high waist circumference, hypertension, glucose intolerance) are frequently present [27].

Lifestyle and Nonpharmaceutical Interventions (Human Studies)

Management of polygenic HTG hinges on **lifestyle modifications** – these can dramatically improve triglyceride levels and reduce risk. Below is a summary of key non-pharmacological interventions, with their documented effects (based on clinical studies in humans):

- **Weight Loss:** Even modest weight reduction has a significant impact. Losing **5–10% of body weight** is associated with about a **20% decrease in triglyceride levels** [31]. Adipose tissue loss reduces free fatty acid flux to the liver and improves insulin sensitivity, thereby lowering VLDL output. For example, in overweight hypertriglyceridemic patients, a 5-10% weight loss through diet/exercise lowered fasting TG by roughly one-fifth on average [31]. Greater weight loss can yield further reductions (often *50% or more TG reduction* in patients who attain a healthy weight from obesity). Weight management is considered **the most effective lifestyle intervention** for HTG [32].

- **Dietary Composition – Reduce Refined Carbohydrates:** Shifting macronutrient balance away from refined carbs and sugars is highly beneficial. Diets lower in carbohydrates (and relatively higher in protein or healthy fats) consistently lead to **lower TG levels** than high-carb diets [33] [34]. In a controlled trial, a **low-carbohydrate diet** (with <15% of calories from carbs) given to individuals with metabolic syndrome *independent of weight loss* produced a significantly greater TG drop than a high-carb diet (TG fell on average by ~20% on the low-carb diet within 4 weeks, versus little change on a high-carb diet) [35] [34]. A meta-analysis of 23 trials likewise found low-carb diets led to an extra **−0.26 mmol/L reduction** in triglycerides (~23 mg/dL) compared to low-fat diets [36] [37]. Mechanistically, cutting refined carbs (white breads, sweets, sugary beverages) reduces hepatic de novo lipogenesis and lowers insulin levels, which in turn curbs VLDL-triglyceride production. *Practical example:* In one case series, simply eliminating sugar-sweetened beverages and desserts for a few weeks in patients with HTG led to TG improvements in the range of 20–30%. Therefore, a **lower-carbohydrate, higher-protein/fat diet** (emphasizing complex carbs over refined starches) is recommended for polygenic HTG [38]. Notably, the **Mediterranean diet** – rich in unsaturated fats (olive oil, nuts) and low in refined carbs – has shown particular benefit. Populations adhering to a Mediterranean pattern have significantly lower TG (one cohort study found ~12% lower TG in those with highest Mediterranean diet adherence) and it's the only diet proven to reduce cardiovascular events [39]. Randomized trials (e.g. PREDIMED) also report **triglyceride reductions** on

Mediterranean diets compared to low-fat diets, thanks to the higher monounsaturated fat intake and omega-3 from fish [39].

- **Alcohol Abstinence:** Alcohol can have a dramatic acute and chronic effect on triglycerides. **Avoiding alcohol** is therefore a key intervention, especially for patients with severe HTG. In alcohol-induced HTG, triglycerides can normalize within weeks of cessation. Clinically, men who consume more than 2 drinks/day (or women >1 drink/day) often show markedly elevated TG; when intake is stopped, TG levels commonly drop by **30–50%** or more (depending on baseline) as hepatic fat synthesis and VLDL secretion decline. For instance, one study demonstrated that moderate alcohol intake significantly **raised** fasting TG by 53% above baseline within hours [8], implying that removing alcohol can reverse that elevation. Patients with **TG >500 mg/dL are advised to completely abstain from alcohol**, as even small amounts can perpetuate dangerous levels [40]. This lifestyle change is crucial to prevent pancreatitis – guidelines stress no alcohol for those with very high TG [40]. In summary, **alcohol restriction/abstinence** in an HTG patient often yields a swift improvement (e.g. a heavy drinker with TG 800 mg/dL might fall to 300–400 mg/dL after a month off alcohol).

- **Fat Intake and Diet Quality:** While lowering carbs is emphasized for moderate HTG, in cases of *extreme* HTG (chylomicronemia), **lowering dietary fat** can also be necessary to reduce chylomicron formation. Patients with TG consistently >1000 mg/dL are sometimes placed on a very low-fat diet (<15% calories from fat) temporarily to prevent pancreatitis, but for most polygenic HTG patients with moderate elevations, an overly low-fat/high-carb diet is counterproductive (it can raise TG). Therefore, the general advice is to **replace refined carbs and saturated fats with healthier fats** (monounsaturated fats like olive oil, omega-3 fats from fish) rather than simply adding carbs. A heart-healthy diet rich in vegetables, fruits, whole grains, lean protein, and fish is ideal [41] [42]. Cutting out sugary drinks, candies, and rapidly digested starches has one of the largest impacts on TG levels.

- **Omega-3 Fatty Acids (Fish Oil):** High-dose marine omega-3 supplementation is a well-established therapy for hypertriglyceridemia. Human trials have shown that around **4 grams per day of EPA/DHA omega-3** can reduce serum triglycerides by **25–30%** on average [43]. For example, a review of 18 controlled studies found 4 g/day of fish oil lowered TG by roughly one-quarter (with higher baseline TG seeing the largest drops) [43]. Omega-3 fatty acids reduce hepatic VLDL-TG synthesis and enhance beta-oxidation of fatty acids. Over-the-counter fish oil at lower doses (1 g/day) has a modest effect (~5–10% TG reduction) [44], whereas prescription-strength doses (2–4 g/day) are used to treat severe HTG [43]. Notably, omega-3 therapy can be an adjunct to lifestyle – for patients unwilling or unable to strictly diet, fish oils can help mitigate TG levels. **Dietary fish intake** is also encouraged: eating fatty fish (salmon, mackerel) at least twice weekly provides omega-3s and has been associated with lower TG and cardiovascular benefits [45].

- **Regular Exercise (Aerobic Training):** Physical activity has a potent triglyceride-lowering effect, both acutely and chronically. Exercise activates skeletal muscle LPL and increases muscle uptake of TG for energy [46]. Even a single session of aerobic exercise can reduce plasma TG the next day by accelerating TG clearance (this acute effect is most pronounced in those with high baseline TG) [46]. Chronic exercise improves insulin sensitivity, thereby decreasing VLDL production over time [47]. *Magnitude:* Consistent aerobic exercise can **lower triglycerides by up to ~20–30%** [48]. A cardiology consensus notes that with the right frequency/intensity (e.g. 150+ minutes of moderate activity per week), TG reductions of **15–30%** are achievable [48]. Indeed, studies suggest a dose-response: the

more one exercises (especially in the "fat-burning" aerobic zone), the greater the TG drop. **Zone 2 cardio** – sustained moderate-intensity exercise that improves fat oxidation – is often recommended for HTG. Patients are advised to engage in at least **30 minutes of moderate exercise (like brisk walking or cycling) on most days** [49]. This helps not only lower TG but also raise HDL and improve overall metabolic health. High-intensity interval training can also reduce TG and is beneficial for insulin sensitivity, though moderate endurance exercise may specifically target TG better by utilizing fat for fuel. In short, **"being active" can cut triglycerides by a quarter or more**, and even incremental increases in activity help (some activity is better than none) [48].

- **Resistance Training:** In addition to aerobic exercise, **strength training** confers benefits for triglyceride levels. A meta-analysis found that progressive resistance training (weight lifting programs) significantly **lowered TG levels** as well [50] [51]. Building muscle mass improves TG uptake from the bloodstream since muscle is a major site of fatty acid combustion. While the TG reduction from resistance exercise alone may be on the order of ~5–10%, combining **aerobic + resistance training** yields the best results. Studies suggest that mixing both types of exercise can reduce TG more than either alone, while also improving other aspects of metabolic syndrome [51] [52]. Therefore, comprehensive lifestyle plans for HTG include *cardio for fat-burning and weight training for muscle-building*. Both contribute to lower triglycerides and better insulin sensitivity.

- **Dietary Fats and Omega-6 Reduction:** Some emerging evidence suggests that replacing some omega-6 polyunsaturated fats with monounsaturated fats can aid TG control. However, the primary focus is on limiting *trans fats* (which raise TG and cause inflammation) and moderating total saturated fat. Ensuring an adequate intake of omega-3 relative to omega-6 is beneficial (e.g. more flaxseed, walnuts, fatty fish). That said, in most individuals, **reducing sugars and losing weight yields a far bigger TG reduction** than tweaking fat subtypes [33].

- **Other Lifestyle Factors:** Avoidance of **smoking** and management of stress can also help, indirectly. Smoking cessation may improve HDL and metabolic parameters that secondarily affect TG. Some small studies note that **time-restricted eating** (limiting meals to a certain window) might lower TG peaks postprandially, though data are early [53]. In all cases, lifestyle therapy is the **first-line treatment** for polygenic HTG and often can bring levels under control without medications [54] [55]. Clinicians typically recommend a comprehensive approach: weight management, dietary counseling (low refined carbs, healthy fats, limit alcohol), and regular physical activity. Only if TG remain persistently high (≥150 mg/dL) after sustained lifestyle changes would adjunctive drug therapy be considered [56] [57]. Encouragingly, the lifestyle measures above not only lower TG but also improve overall cardiovascular risk and metabolic well-being.

(Supporting data from human studies: Mediterranean diet interventions, for example, consistently show TG lowering in the range of ~10–20% [39]; omega-3 prescription trials show ~25–30% TG reduction [43]; a 2021 guidelines review states weight loss is most effective lifestyle measure (5–10% weight = ~20% TG drop) and exercise can reduce TG up to 30% [31] [48]. All these nonpharmacologic strategies are derived from clinical trials, cohort studies, and meta-analyses in humans.)

Transient Factors and Special Cases Affecting TG Levels

Certain **acute conditions and life events** can cause sudden swings in triglyceride levels, especially in those with a polygenic predisposition. These transient or situational factors often **unmask or worsen hypertriglyceridemia**:

- **Acute Infection or Inflammation (e.g. COVID-19):** Severe infections and systemic inflammatory states can precipitate a spike in triglycerides. During acute COVID-19, for instance, some patients have developed **severe hypertriglyceridemia** – case reports describe COVID-19 triggering TG > 1000 mg/dL and even pancreatitis in predisposed individuals [58] [59] . The inflammation and cytokine storm in COVID can suppress LPL activity (a **transient inhibitor of LPL** has been observed post-COVID) [60] , leading to reduced clearance of TG-rich lipoproteins. Additionally, treatments like high-dose corticosteroids or certain antivirals can contribute to HTG. This phenomenon isn't unique to COVID; any **acute inflammatory illness** (sepsis, severe influenza, etc.) tends to raise TG levels as part of the "acute phase" response (the liver shifts to producing VLDL and other substrates). In most cases, these effects are **reversible** – as the infection resolves, triglycerides fall back down. Nevertheless, clinicians must watch for **acute pancreatitis** when an infection drives TG into extreme ranges. For example, a patient with baseline TG ~300 mg/dL might temporarily shoot above 1000 mg/dL during severe COVID-19, then return to ~300 after recovery. Awareness of this link is important, as treating the inflammation (and possibly using insulin infusions or plasmapheresis in critical HTG) can prevent pancreatitis [61] .

- **Physical Inactivity and "Burnout" Periods:** Cessation of regular exercise – for example, due to injury, lockdown, or burnout – can **acutely elevate triglyceride levels**. Exercise has an immediate TG-lowering action by boosting LPL; when someone goes from being active to suddenly sedentary, that benefit is lost [46] . Studies show that much of exercise's effect on TG is **acute – within 24–48 hours** [46] . Thus, even a short period of inactivity can lead to higher TG until activity is resumed. A practical example is a patient with polygenic HTG who normally jogs daily to keep TG ~200 mg/dL; if they stop exercising for a week (due to, say, work burnout or illness), their TG might rise to 300–400 mg/dL. "Burnout-related inactivity" often coincides with poor diet and stress, compounding the issue. Chronic **stress and burnout** can elevate cortisol, which promotes adipose tissue lipolysis and hepatic gluconeogenesis – this can increase VLDL secretion and worsen insulin resistance, both driving TG upward. In essence, **sedentary lifestyle and stress** create a metabolic milieu favoring HTG [17] . The good news is that reintroducing even moderate physical activity can rapidly improve the profile. For example, *case studies* have documented that a single bout of aerobic exercise can lower next-day triglycerides by ~20% in previously sedentary individuals [46] . In summary, **periods of inactivity (bed rest, desk-bound weeks, etc.) reliably raise TG**, especially in those with underlying HTG, while resumption of exercise has an immediate corrective effect.

- **Metabolic and Endocrine Disturbances:** Intercurrent metabolic conditions can transiently push triglycerides to extreme levels. A prime example is **poorly controlled diabetes mellitus**. In uncontrolled diabetic states (especially type 1 diabetes with insulin omission or diabetic ketoacidosis, and severe insulin-resistant type 2), insulin activity is low – since insulin normally stimulates LPL and suppresses fat release from adipose, its absence causes a flood of fatty acids to the liver and a halt in LPL function. The result can be **drastic hypertriglyceridemia**. Indeed, in diabetic ketoacidosis TG levels >1000 mg/dL are sometimes seen, resolving once insulin therapy is instituted. In individuals with polygenic HTG, if they become diabetic or their diabetes decompensates, TG can acutely climb

from moderate to severe range. Restoring euglycemia and insulin sufficiency will typically bring TG down. **Hypothyroidism** is another endocrine issue: an underactive thyroid slows metabolism, including lipid metabolism, and often causes elevation in cholesterol and triglycerides. If a patient with HTG develops hypothyroidism, their TG might rise further until the thyroid is treated [62]. The **mechanism** involves reduced hepatic LDL receptor activity and perhaps diminished LPL activity in hypothyroid states. **Corticosteroid excess (Cushing's syndrome or high-dose steroid therapy)** also induces hypertriglyceridemia by increasing hepatic VLDL production and causing insulin resistance [63]. For example, a patient on prednisone may see TG jump significantly during therapy. Fortunately, these effects are transient: treating the hypothyroidism or tapering off steroids leads to improvement in the lipid profile. In summary, **any abrupt change in metabolic control – be it glucose control, thyroid function, or steroid hormones – can acutely impact TG levels**. Clinicians managing HTG patients should check for these reversible factors (e.g. by screening for hypothyroidism or suboptimally controlled diabetes) [64] [65].

- **Hormonal Shifts (Estrogen and Others):** Hormonal changes, especially involving estrogen, can transiently raise triglycerides. **Pregnancy** is a classic example: during the second and third trimester, estrogen levels rise dramatically and hepatic lipoprotein synthesis increases. It's normal for pregnant women to have higher TG, but those with underlying polygenic HTG can reach very high values in late pregnancy. In fact, *gestational hypertriglyceridemia* (TG > 500 mg/dL in pregnancy) can occur and may lead to pancreatitis, usually in the third trimester [66]. Triglycerides typically peak around the time of delivery (often 2–3 times pre-pregnancy levels) and then drop postpartum. If a woman has a genetic predisposition, she might start pregnancy with TG ~150 and end with TG ~400–600 mg/dL; if extremely predisposed, she could even exceed 1000 mg/dL late in pregnancy, necessitating a low-fat diet or plasmapheresis to prevent pancreatitis. After childbirth (and especially after breastfeeding, when hormones normalize), TG usually return to baseline. **High-dose estrogen therapy** (such as oral contraceptives with older high estrogen formulations, or hormone replacement in some cases) can similarly raise TG. Estrogen increases VLDL production and can overwhelm a predisposed individual's clearance capacity [67]. For instance, cases of young women with familial HTG experiencing TG spikes on birth control pills have been documented. **Menopause** is another transition – loss of estrogen might slightly raise LDL and TG – but the effect on TG is usually less pronounced than the effect of exogenous estrogen or pregnancy. **Growth hormone deficiency or excess** can also alter TG, but those are rare scenarios. Overall, **hormonal milieu changes are important transient modulators**: clinicians should be vigilant during pregnancy or when starting hormonal medications in patients with known HTG. In pregnant patients with polygenic HTG, periodic monitoring of TG is warranted, and if TG climb too high, interventions (like a very low-fat diet or fibrate medication) may be needed to avert pancreatitis. Fortunately, post-pregnancy levels usually fall back, reflecting the **transient nature of estrogen-induced HTG**.

- **Other Special Cases: Acute weight gain** (e.g. rapid gain due to overeating or certain medications) can spike TG in the short term, as the liver ramps up VLDL output to store surplus calories as fat. **Medications** such as isotretinoin, some antipsychotics, beta-blockers, protease inhibitors for HIV, etc., can cause *acute* rises in TG – if a patient with polygenic HTG starts one of these drugs, their TG could jump from moderate to very high in a matter of weeks [63]. These drug-induced effects are generally reversible upon discontinuation. Even **acute stress or illness** (as mentioned earlier) can transiently worsen HTG, as can **dietary indiscretions** (the classic "holiday effect" – after a week of feasting and drinking, patients often have a TG surge). Finally, **burnout and sleep deprivation** can indirectly raise TG via hormonal stress responses and weight gain – for instance, elevated nighttime

cortisol and disrupted circadian rhythm are linked to higher VLDL levels. Each of these scenarios underscores that triglycerides are *dynamic* and sensitive to physiological changes. For patients known to have polygenic HTG, it's important they recognize these triggers. If their TG levels suddenly worsen, one should investigate recent lifestyle changes, new illnesses, or medications as potential causes.

In conclusion, polygenic primary hypertriglyceridemia is a complex interplay of genetic predisposition and environmental factors. Its mechanisms involve both overproduction and reduced clearance of triglyceride-rich lipoproteins. The phenotype ranges widely from mild to severe, influenced by diet, weight, alcohol use, and other habits. Lifestyle interventions – weight loss, low-refined-carb diet, abstaining from alcohol, omega-3 supplementation, and exercise – are highly effective in lowering triglycerides (often yielding 20–50% reductions or more) and are the cornerstone of management [31] [43]. A number of transient conditions can acutely exacerbate HTG (such as infections, pregnancy, uncontrolled diabetes, or inactivity), and clinicians must manage these to prevent complications like pancreatitis. By combining genetic insight with aggressive risk factor modification, most patients with polygenic HTG can achieve safe triglyceride levels and substantially mitigate long-term risks [68] [69].

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