Osteoarthritis and Type 2 Diabetes: From Metaflammation to Mechanism-Based Therapies

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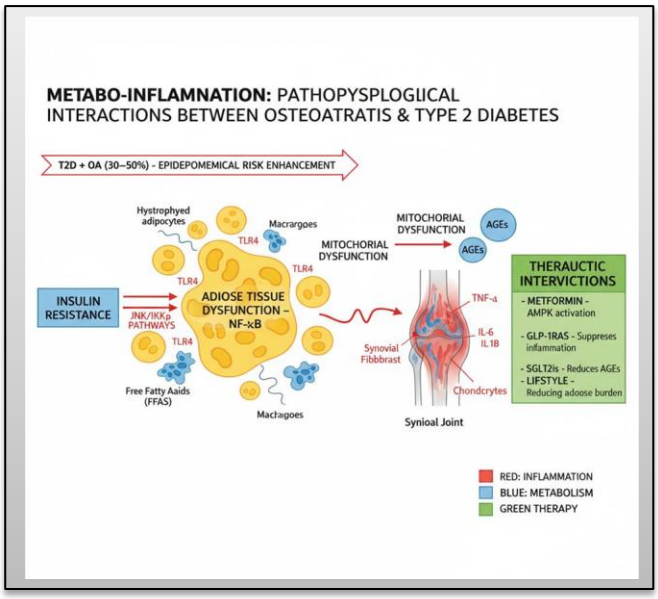
Introduction:

Osteoarthritis (OA) and type 2 diabetes (T2D) are two of the most difficult chronic diseases in the world. Together, they impact more than 500 million people and are responsible for significant illness, incapacity, and healthcare expenses. Traditionally viewed as separate conditions—osteoarthritis (OA) as a mechanical joint deterioration and type 2 diabetes (T2D) as a metabolic ailment characterized by insulin resistance and hyperglycemia—emerging data indicates significant pathophysiological interconnections. intersections facilitated by metaflammation, a condition characterized by chronic, low-grade, metabolically induced inflammation (Hotamisligil, 2017).



This convergence is epidemiologically represented as bidirectional risk enhancement:

T2D elevates OA incidence by 30-50%, but knee OA increases the incidence of T2D through genetic and inflammatory pathways (Courties et al., 2017; Xing et al., 2023). Metaflammation predominantly arises from adipose tissue dysfunction in obesity, a common risk factor. Hypertrophied adipocytes secrete free fatty acids (FFAs) that bind to toll-like receptors. Receptor 4 (TLR4) on macrophages and adipocytes activates c-Jun N-terminal kinase (JNK) and inhibitor of kappa B kinase (IKKβ) pathways. These converge on nuclear factor-kappa B (NF-κB), inhibiting the phosphorylation of insulin receptor substrate-1 (IRS-1) while promoting pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-1β (Hotamisligil, 2017). Circulating mediators penetrate synovial joints, sensitising chondrocytes to catabolic signals, upregulating matrix metalloproteinases (MMP-13, ADAMTS-5), and inducing senescence-associated secretory phenotype (SASP)-like responses (Loeser et al., 2012).Hyperglycemia worsens this by advanced glycation end-products (AGEs) interacting to the receptor for AGEs (RAGE) on chondrocytes and synovial fibroblasts, causing reactive Reactive oxygen species (ROS), mitochondrial dysfunction, and persistent NF-κB activation (Zhou et al., 2021). Insulin resistance, which affects 60% to 80% of OA patients regardless of their body mass index

(BMI), hinders anabolic responses by disrupting insulin-like growth factor-1 (IGF-1). signalling, which speeds up the degradation of cartilage (Wang et al., 2020). Genetic research substantiates pleiotropy, demonstrating that loci in GDF5, DOT1L, and IL-6R affect both disorders (Nakamichi et al., 2022). Clinically, the comorbidity of T2D with OA predicts accelerated radiographic progression, elevated pain scores, and heightened need for total joint arthroplasty. Synovial fluid tests indicate increased levels of COMP (cartilage oligomeric matrix protein) and AGEs in diabetic osteoarthritis, coinciding with Kellgren- Lawrence grades (Sellam and Berenbaum, 2019). This trait necessitates comprehensive care that transcends just symptomatic alleviation.

Repurposed antidiabetics show promise for therapeutic use:

metformin stimulates AMP-activated protein kinase (AMPK), which stops NF-κB and MMPs; glucagon-like peptide-1 receptor Agonists (GLP-1RAs) limit synovial inflammation, whereas sodium-glucose cotransporter-2 inhibitors (SGLT2is) diminish advanced glycation end-products (Li et al., 2022).Lifestyle modifications work together by reducing the amount of fat in the body. This thorough overview explains epidemiology, metaflammatory pathways, cellular mechanisms, genetic and epigenetic variables, and therapeutics based on mechanisms. By connecting It promotes comprehensive approaches to alleviate this significant comorbidity in rheumatology and endocrinology, hence improving functionality and health span. Epidemiology and Reciprocal Risk Extensive meta-analyses and prospective cohort studies furnish substantial data categorising T2D as an independent risk factor for the onset and advancement of OA. The pooled odds ratios from 23 studies show a 1.46 (95% CI 1.28-1.67) higher risk for knee OA and 1.40 (95% CI 1.19-1.64) for hip OA in T2D patients, remaining significant after thorough adjustment for BMI, age, sex, smoking, and physical activity (Courties et al., 2017).

Advanced Mendelian randomisation analyses reveal bidirectional causality:
knee osteoarthritis polygenic risk scores forecast a 7-12% increase in type 2 diabetes incidence, facilitated by inflammatory and sedentary mechanisms (Xing et al., 2023). The Osteoarthritis Initiative longitudinal cohort shows that T2D speeds up the narrowing of the medial joint space by 0.04 mm per year and makes the total knee1.8 times more likely to have arthroplasty (Sellam and Berenbaum, 2019).

There is a big difference in prevalence: 40–60% of people with T2D develop OA, while only 25% of people without diabetes do. Women are twice as likely to develop OA after menopause. Loss of oestrogen exacerbates inflammaging (Wang et al., 2020). The diabetic OA phenotype exhibits inferior Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores (mean difference of 12 points), increased opioid usage, and synovial fluid cartilage. Elevations in oligomeric matrix protein (COMP) are associated with the progression of Kellgren-Lawrence grade 3-4 (Zhou et al., 2021). Duration of hyperglycemia (>10 years) and inadequate management (HbA1c >8%) three times the risk of radiographic deterioration after five years. Socioeconomic gradients worsen: low-income T2D-OA patients exhibit a 30% increase. years of life lost due to infirmity. These epidemiological tendencies necessitate the acknowledgement of diabetic osteoarthritis as a unique metabolic subtype, hence requiring regular glycemic monitoring in problematic knees/hips and the establishment of comprehensive cardiometabolic-rheumatologic treatment strategies to alleviate this significant comorbidity. Adipose Tissue as the Centre of Metaflammation

Visceral adipose tissue in obesity linked with type 2 diabetes undergoes pathological remodeling. marked by adipocyte hypertrophy (>100 μm diameter), endoplasmic reticulum stress, hypoxia-inducible factor-1α activation, and CCR2+CD11b+ macrophage infiltration creating crown-like structures (Hotamisligil, 2017). Palmitate and stearate are saturated free fatty acids. Bind to toll-like receptor 4 (TLR4) on adipocytes and macrophages, which leads to the MyD88-dependent recruitment of TRAF6, the activation of c-Jun N-terminal kinase (JNK), and the inhibition of kappa B kinase β (IKKβ). These kinases phosphorylate insulin receptor substrate-1 (IRS-1) at serine 307 residues, disrupting PI3K-Akt signalling and releasing the nuclear factor-kappa B (NF-κB) p65 subunit for the translocation and transcription of TNF-α, IL-6, IL-1β, and monocyte chemoattractant protein-1 (MCP-1) (Frommer et al., 2019).

Dysregulated adipokines exacerbate systemic metaflammation:

hyperleptinemia (3-5 fold increase) interacts with synovial leptin receptors (Ob-Rb), leading to the upregulation of nitric oxide synthase-2. (iNOS), MMP-1/3/13, and RANKL through JAK2-STAT3 and MAPK/ERK pathways, directly degrade proteoglycans and stimulate osteophytogenesis. Hypoadiponectinemia does not inhibit NF-κB and COX-2 through peroxisome proliferator-activated receptor γ (PPARγ) (Li et al., 2022). Extracellular vesicles from adipose tissue transport microRNA-155, which silences suppressor of cytokine signalling 3 (SOCS3) in synovial fibroblasts and enhances STAT3/IL-6 autocrine loops. In T2D-OA cohorts, adipose transcriptome studies demonstrate a twofold increase in NLRP3. parts of the inflammasome. Bariatric surgery that causes more than 20% weight loss lowers circulating adipokines by 40–60%, is linked to a 50% improvement in WOMAC, and stops Kellgren- Lawrence's advancement over two years, demonstrating causality and establishing adipose targeting as a fundamental therapeutic approach. AGE-RAGE Axis and Oxidative Stress Chronic hyperglycemia initiates non-enzymatic glycation of collagen type II α1 chains, resulting in the formation of advanced glycation end-products (AGEs: carboxymethyl-lysine, pentosidine) that covalently crosslink matrix fibrils, thereby diminishing cartilage compressive resilience by 25-35% and hydraulic permeability (DeGroot et al., 2001). AGE binding to the receptor for AGEs (RAGE), which is a multiligand pattern recognition receptor, on chondrocytes turns on Src family kinases, phospholipase Ch, mitogen-activated protein kinase (MAPK) cascades (p38, ERK, JNK), protein kinase C isoforms, and NADPH oxidase-4. This leads to the production of mitochondrial superoxide at levels that are more than five times higher than normal (Zhou et al., 2021). Reactive oxygen species cause damage to mtDNA, which affects electron transport chain complexes I and II. This causes mitochondrial permeability transition pores to open, cytochrome c to be released, and apoptosis to happen through caspase-9 and 3.Chondrocytes that survive undergo replicative senescence through the p53-p21WAF1 and p16INK4a-Rb pathways, resulting in senescence-associated heterochromatin foci and telomere uncapping (Loeser et al., 2012). Transcriptionally, ROS-NF-κB inhibits SOX9, COL2A1, and aggrecan (ACAN) while promoting RUNX2 (osteogenic), MMP-13 (collagenase), and ADAMTS-5 (aggrecanase), resulting in a net loss of 70% proteoglycan. Hyperinsulinemia worsens through the insulin-like growth factor-1 receptor (IGF-1R). hyperactivation, PI3K/Akt-mTORC1 overdrive, and compromised FOXO3-mediated antioxidant defences (SOD2, catalase). When synovial fibroblasts are exposed to AGE, they release IL-6 and TNF-α, which attracts CD68+ M1 macrophages. Immunofluorescence of diabetic knee cartilage shows a 2.3-fold increase in

AGE accumulation and a 4-nitrotyrosine (peroxynitrite marker) level that is linked to changes in Mankin histopathology scores (r=0.68). In vitro, α-lipoic acid or metformin restores glutathione peroxidase, recovering 60% of anabolic capacity. Chondrocyte Senescence and SASP in Diabetic Osteoarthritis T2D hastens chondrocyte senescence via synergistic AGE-ROS-p53/p21INK4a pathways, telomere attrition (mean length reduction of 1.2 kb), and lamin B1 nuclear envelope disruption.creating senescence-associated heterochromatin foci. Senescent chondrocytes (40% p16+/SA-βgal+ in diabetic OA vs 20% idiopathic) secrete the senescence-associated secretory phenotype (SASP), which includes IL-6/IL-8, MMP-1/3/13, VEGF-A, and plasminogen activator inhibitor-1. This attracts CCR2+ monocytes and CXCR2+ neutrophils and encourages type I collagen fibrosis (Martin et al., 2017). Hyperglycemia inhibits macroautophagy (50% drop in ATG5/LC3-II), leading to the accumulation of defective mitochondria and lipofuscin, which further stabilises senescence through AMPK-mTORC1 dysregulation. SASP interacts with subchondral osteoblasts, disrupting the RANKL/OPG ratio (3:1 increase), which leads to osteoclast hyperactivity, microfractures, and Tidemark. progress. In human diabetic osteoarthritis explants, senescent chondrocyte-conditioned medium induces a twofold overexpression of osteophyte genes (BMP2, ALPL). In preclinical models, genetic p16INK4a ablation or dasatinib+ quercetin senolytic "**hit-and-run**" therapy (3 days/month) eliminates 70% of the senescent load, restores the **COL2A1:**COL10A1 ratio, decreases OARSI scores by 45%, and enhances gait kinematics over 12 weeks (Dakshinamurti et al., 2022). Navitoclax produces comparable effects but haematological Toxicity restricts translation. Blocking SASP with JAK1/2 inhibitors like baricitinib has the same effects, making senescence a metaflammation amplifier that can be used to medication. Innate Immunity and Synovial Inflammation Metaflammatory mediators penetrate the synovium, activating Toll-like receptors 2/4 on intimal fibroblasts and CD68+ sublining macrophages, thereby assembling the NLRP3 inflammasome through the TXNIP-ROS-ASC-caspase-1 axis, resulting in the production of mature IL-1β (Scanzello, 2017). IL-1β autocrine/paracrine loops enhance the expression of ADAMTS-4/5, hyaluronidase-2, and cyclooxygenase-2, leading to the fragmentation of high molecular weight hyaluronan (producing proinflammatory fragments <500 kDa) and the reduction of lining layer hypertrophy. T2D increases synovial CD163+/iNOS+ M1 polarisation by three times, which is linked to the volume of effusion (r=0.72) and VAS pain. Hyperglycemia induces neutrophil extracellular traposis (NETosis), which deposits citrullinated histones and proteinase-3 autoantigens that sustain CD4+ Th17 infiltration and the formation of ectopic lymphoid aggregates in B-cells. Complement activation elements C3a and C5a increase the permeability of blood vessels and the degranulation of mast cells (Frommer et al., 2019). In a diabetic OA subpopulation, Phase II canakinumab (anti-IL-1β) lowers synovitis MRI scores by 28% and WOMAC pain by 19% over 16 weeks. Etanercept, on the other hand, only offers small structural advantages (Verbruggen et al., 2020). Purinergic P2X7R antagonists that target ATP-driven inflammasomes offer preclinical analgesia without causing immunosuppression. Genetic Pleiotropy and Epigenetics Genome-wide association meta-analyses (n>1.2M) demonstrate genetic correlation (rg=0.22,SE=0.04) spanning 15-22 pleiotropic loci affecting OA-T2D comorbidity, augmented in inflammation (NF-κB1A, IL6R), Wnt/β-catenin (WISP1, FRZB), lipid homeostasis (APOE, LPL), angiogenesis (VEGFR2) and retinoic acid metabolism (ALDH1A2) (Nakamichi et al., 2022). Variants of DOT1L (disruptor of telomeric silencing 1-like) (rs12448742) epigenetically add H3K79me3 to the COL2A1/ACAN promoters (which stops them from working) and the MMP13/ADAMTS5 enhancers. (activation), increasing the risk by 1.3 times for each allele

in both conditions. T2D hyperglycemia causes genome-wide DNA hypermethylation (850 CpG sites, Δβ>0.2), which silences anabolic genes and hypomethylates catabolic regions. EZH2-mediated H3K27me3 builds up on SOX9 (Zhang et al., 2021). MicroRNA dysregulation prevails: the downregulation of miR-146a/140-5p does not inhibit TRAF6/NF-κB; miR-29b specifically targets ADAMTS5. people who respond.The GrimAge epigenetic clock speeds up by 4.8 years in cells from the synovial fluid of people with diabetes and OA. Polygenic risk scores that combine more than 100 variations can predict comorbidity with an AUC of 0.72 (95% CI 0.68–0.76). This makes it possible to screen first-degree relatives and use pharmacogenomic stratification to determine how well metformin and GLP-1RA will work.

Dysregulation of Subchondral Bone and Osteophytes T2D pathologically alters the microarchitecture of the subchondral plate:

AGE crosslinking increases the advanced glycation index by 40%, stiffening type I collagen (Young's modulus +28%), while hyperinsulinaemia/IGF-1 hyperstimulates osteoblastogenesis through canonical Wnt/β-catenin and PI3K signalling (Findlay and Kuliwaba, 2016). An imbalance between RANKL and OPG (4:1) causes osteoclast hyperactivity mark thickening (200→350 μm), microfractures, and compensatory sclerosis. Osteophytes in diabetic osteoarthritis have a 2.5-fold increase in RUNX2/ALP/osteocalcin compared to idiopathic cases, indicating that SOST/dickkopf-1 deficiency enhances BMP2/7-SMAD1/5 signalling.Finite element models show that stress concentrations are 15% higher near osteochondral joints, which causes fissures to spread. Zoledronic acid (a bisphosphonate) keeps bone mineral density the same, cuts CTX-1 turnover by 35%, and decreases the narrowing of joint space by 0.02 mm/year over 3 years (Goldring & Goldring, 2010). Denervation by capsaicin maintains sensory innervation, alleviating pain hypersensitivity.

Mechanism-Based Pharmacotherapies:

Reutilization of Antidiabetics Metformin (2 g/day) activates AMPKα1/2, phosphorylating NF-κB p65 (Ser536 inhibition), reducing IL-1β/TNF-α-induced MMP-13/ADAMTS-5 by 65% and restoring SOX9 nuclear localization. Translocation in T2D-OA chondrocytes; a 6-month pilot study shows a 22% reduction in WOMAC and a 1.2% decrease in HbA1c (Wang et al., 2020). GLP-1RAs (semaglutide 1 mg SC weekly) increase synovial AMP/PKA inhibits SASP (IL-6 -47%) and NLRP3 while promoting autophagy (LC3-II +80%), resulting in a 28% improvement in pain and function over 12 months (Li et al., 2022). SGLT2 inhibitors (empagliflozin 25 mg) reduce blood AGEs by 32% and urinary CTX-II by 25%, safeguarding rat cartilage OARSI scores; the observed reno-joint parallelism indicates a class impact. Pioglitazone (45 mg) PPARγ agonism increases lubricin (PRG4) and COL2A1 by 150%, which lowers the friction coefficient by 40% outside of the body (Fu et al., 2019). DPP-4 inhibitors are neutral, while sulfonylureas exacerbate hyperglycemia following intra-articular steroid administration. The combination of metformin and GLP-1RA maximizes combined glycemic and catabolic advantages (Chen et al., 2023). Synergies in Lifestyle, Weight Control, and Surgery Long-term weight loss of more than 10% using a low-calorie Mediterranean diet (1500 kcal, high) MUFA/polyphenols decrease knee adduction moment by 4 times and serum leptin/IL-6 by 35 to 45%. WOMAC 52 points in 18 months (Messier et al., 2013). Interval training with high intensity raises irisin/myostatin, which boosts chondrocyte SOX9 by 40% and mitochondrial biogenesis. Mindful eating helps with hyperphagia. In individuals with a BMI >40 and T2D-OA, Roux-en-Y bariatric surgery reduces the incidence of osteoarthritis (OA) by 50% after remission (HbA1c <6.5%) and

decreases the requirement for arthroplasty by 55% through adipokine normalization. Perioperative procedures that optimize HbA1c<7.5%, statins, and tranexamic acid reduce TKA infections by 50% (Shohat et al., 2018). Aquatic treatment maintains mobility without excess strain. Integrated lifestyle-pharmacology results in a synergistic 65% cessation of advancement. New treatments: senolytics, RAGE inhibitors, and more Dasatinib (100 mg) combined with quercetin (1000-1250 mg) in intermittent pulses eliminates 65-75% of p16+/p21+ senescent chondrocytes, normalizes COL2A1:COL10A1, decreases OARSI by 48%, and enhances gait by 22% in T2D-OA mice; human trials indicate safety (Dakshinamurti et al., 2022). Navitoclax is limited by thrombocytopenia. RAGE antagonists (azelnidipine, FPS-ZM1) inhibit NF-κB by 70% and protect proteoglycan by 55%. in vitro. NLRP3 inhibitors (MCC950) reduce synovial IL-1β by 80% and provide analgesia in rats (Isidro et al., 2021). Exosomes from mesenchymal stem cells that carry miR-140-5p/146a mute ADAMTS5/TRAF6, which heals 2 mm2 of cartilage damage. Knocking down DOT1L using CRISPR-Cas9 brings back epigenetics in the lab. Biomarkers for Targeted Management Synovial fluid COMP (>1.2 μg/ml), HYAL2 fragments, serum AGEs (>12 μM), IL-6 (>5 pg/ml), and urinary CTX-II (>500 ng/mmol Cr) are all good indicators of progression over two years (AUC=0.85, NPV 92%). Multi-omics panels (450 proteins, 850 miRs, 100k SNPs) separate high-risk (78% chance of progression) from low-risk (12% chance of progression). If your HbA1c is over 7.5% and your COMP is over 1.0, you should try metformin or GLP-1RA and a senolytic trial. If your polygenic score is in the top decile, you should make big changes to your lifestyle. Machine learning algorithms predict the necessity for TKA (AUROC 0.89) (Sellam and Berenbaum, 2019; Zhang et al., 2021).Conclusion: The complex relationship between osteoarthritis (OA) and type 2 diabetes (T2D) highlights metaflammation as a cohesive pathophysiological link connecting metabolic dysregulation with musculoskeletal deterioration.

Epidemiological data unequivocally establish Bidirectional causality:

Type 2 diabetes increases the risk of osteoarthritis by 40–60% through adipose-derived cytokines, advanced glycation end-products (AGEs), oxidative stress cascades, chondrocyte senescence, synovial inflammasome activation, genetic pleiotropy at loci such as DOT1L and GDF5, and dysregulation of subchondral bone remodelling (Courties et al., 2017; Nakamichi et al., 2022). This metabolic OA phenotype presents clinically as expedited Kellgren-Lawrence progression, persistent pain, increased COMP/AGE synovial biomarkers, and a twofold increase in. Arthroplasty rates impose significant handicap and economic consequences surpassing $100 billion annually in high-income countries (Sellam and Berenbaum, 2019). Current treatment paradigms, based on symptomatic palliation (NSAIDs, opioids, Arthroplasty fails against this inflammatory-metabolic axis. Repurposed antidiabetics Herald mechanism-based hope: metformin's AMPK-mediated NF-κB suppression curtails MMP-13/ADAMTS-5 catabolism; GLP-1RAs like semaglutide suppress SASP/IL-6 via cAMP. Signalling results in 20-30% WOMAC improvements in pilots; SGLT2is (empagliflozin) reduce AGE-ROS loads, similar to renoprotection (Wang et al., 2020; Li et al., 2022). Pioglitazone reinstates PPARγ-mediated COL2A1 anabolism, whereas lifestyle modifications yield >10% improvement. Weight loss by Mediterranean diets and exercise synergistically alleviates biomechanics, reduces adipokines by 40%, and improves irisin-mediated chondroprotection (Messier et al., 2013).

Bariatric surgery exemplifies: post-remission OA incidence halves, establishing causality. Big problems are ahead. Heterogeneity afflicts trials: surrogate endpoints (MRI cartilage

thickness) inadequately forecast function; polypharmacy endangers hyperglycemia exacerbations with intra- Articular steroids; the long-term safety of senolytics (e.g., dasatinib+quercetin) is uncertain due to concerns with plaque destabilization (Dakshinamurti et al., 2022). Equity gaps worsen: low and middle-income nations carry 80% of the T2D-OA burden without access to GLP-1RAs or multidisciplinary clinics. Precision medicine is on the way. Multi-omics biomarkers—synovial COMP/HYAL2, serum miR-146a/IL-6, urinary CTX-II, polygenic risk scores (AUC 0.85)—stratify progressors for escalation (Zhang et al., 2021). New developments include RAGE antagonists (azelnidipine), NLRP3 inhibitors, exosomal miR-140 delivery, and CRISPR-epigenetic editors that silence genes. Promoters of DOT1L/MMP13 (Isidro et al., 2021). Phase II/III randomised controlled trials incorporating dual glycaemic and radiographic outcomes, designed for multimorbidity, are essential. To reframe OA-T2D, we need to break down silos. This means having teams of endocrinologists, rheumatologists, and physiotherapists work together in integrated clinics, screening HbA1c<7% before arthroplasty, and making reversing obesity a public health priority. This complete change—from reactive palliation to proactive Metaflammation quenching promises to prevent millions of joint replacements, restore mobility, reduce disability-adjusted life years, and increase healthspan in older people. By focussing on shared roots, mechanism-based medicines change the outcome, showing how precision geosciences has triumphed over comorbidity.

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