Estrogen therapy and improvements in multiple clinical measures in trans gender women

Paula Aurélie Fisher

White Paper

Estrogen therapy and improvements in multiple clinical measures in Transgender Women

by Paula Aurélie Fisher

This educational white paper summarizes themes from the peer-reviewed literature identified in this conversation, these being available as references at the summary of this white paper. It distinguishes established clinical findings from biologically plausible hypotheses and areas of ongoing research.

The primary reason for producing this is determine the viability of estrogen-based therapy to have a noticeable effect on various clinical conditions and outcomes so far as kidney function, eye health and general laboratory results.

Some trans-gender patients reported noticing positive changes in some or many of their clinical conditions and laboratory results noticeably during the early stages of starting HRT (Hormone-Replacement-Therapy), specifically Estrogen.

It's also to be noted than many surveyed trans-gender women have noticed during their lifetime a physiological difference in their overall appearance from the cis-gender counterparts. This includes, but not limited to,

- pubescent growth of typically feminine breast tissue,
- wider than normal hips,
- slimmer general body shape.
- Sensitivity to estrogen post-teen,
- lack of testosterone sensitivity post-teen.

Given that current medical studies indicate strong evidence for in-utero development of gender incongruence, it would therefore make a high probability that a trans-gender woman's brain would then adapt easier to estrogen-based therapy. The brain after-all is the control center for triggering hormonal cycles.

This paper is also the selected evidence related to the below informative graphics …

ESTROGEN THERAPY: ASSOCIATIONS WITH IMPROVED LAB VALUES AND CLINICAL OUTCOMES IN TRANS-WOMEN

MEDICAL PERSPECTIVE – CURRENT EVIDENCE AND BIOLOGICAL PLAUSIBILITY

Estrogen has widespread effects on vascular, metabolic, renal, hematologic, ocular and neuroendocrine systems. These effects can contribute to improved laboratory values and clinical outcomes.

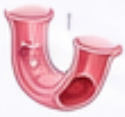
KEY POINT

Many improvements are associations supported by biological mechanisms. Causation for specific diseases has not been conclusively proven in large clinical trials for transgender women, but evidence is growing.

OVERALL PATTERN OF IMPROVEMENT REPORTED

Improved Lab Values → Improved Clinical Markers → Better Quality of Life → Reduced Long-term Risk

1. BIOLOGICAL MECHANISMS OF ESTROGEN

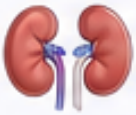


VASCULAR PROTECTION

Improves endothelial function, increases nitric oxide, reduces oxidative stress and inflammation.

METABOLIC EFFECTS

Improves insulin sensitivity in some individuals, modulates lipid metabolism and body composition.



RENAL & ELECTROLYTE EFFECTS

Modulates renin–angiotensin–aldosterone system, may reduce proteinuria and inflammation.

ANTI-INFLAMMATORY & ANTIOXIDANT

Downregulates pro-inflammatory cytokines and reduces systemic inflammation.

NEUROENDOCRINE & PSYCHOLOGICAL

Reduces stress, anxiety and dysphoria, improves sleep and autonomic balance.

These mechanisms create a systemic environment that can support improved health.

2. EFFECTS ON COMMON LABORATORY VALUES

	BEFORE ESTROGEN	AFTER ESTROGEN	CLINICAL SIGNIFICANCE
HEMATOLOGY Hemoglobin / Hematocrit Decrease toward female reference range	17.0 g/dL 50%	→ 13.5 g/dL 40%	Reduces blood viscosity and thrombotic risk over time.
KIDNEY FUNCTION Creatinine / eGFR Often improves or stabilizes	Creatinine 1.2 mg/dL eGFR 68	→ Creatinine 0.9 mg/dL eGFR 88	May reflect improved renal hemodynamics and/or reduced muscle mass (lower creatinine production). Monitor with cystatin C.
LIPID PROFILE LDL, HDL, Triglycerides Favorable lipid modulation	LDL 140 HDL 45 TG 180	→ LDL 95 HDL 65 TG 110	Improved cardiovascular risk profile.
GLUCOSE METABOLISM Fasting Glucose / HbA1c Improved insulin sensitivity in some	HbA1c 7.8%	→ HbA1c 6.5%	Better glycemic control reduces microvascular complications.
INFLAMMATORY MARKERS CRP, IL-6, TNF-α Decrease over time	CRP 6.0 mg/L IL-6 4.5 pg/mL	→ CRP 2.2 mg/L IL-6 1.8 pg/mL	Lower systemic inflammation supports vascular and metabolic health.
LIVER ENZYMES AST, ALT, GGT May improve or normalize	ALT 48 U/L AST 40 U/L	→ ALT 28 U/L AST 25 U/L	Improved liver metabolism and reduced steatosis risk.

Note: Individual responses vary. Results depend on dose, duration, genetics, baseline health and co-existing conditions.

3. IMPACT ON CLINICAL OUTCOMES

CARDIOVASCULAR HEALTH
Improved lipid profile, blood pressure and vascular compliance reduce long-term cardiovascular risk.

DIABETIC RETINOPATHY
Better glycemic control, reduced inflammation and improved retinal microcirculation may slow progression and, in some cases, lead to improvement.

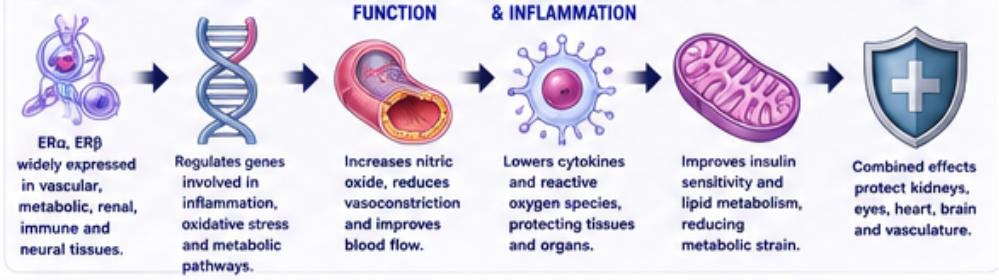
KIDNEY HEALTH
Reduced inflammation, improved vascular function and better blood pressure control may stabilize or improve kidney function.

MENTAL HEALTH & WELL-BEING
Reduced dysphoria, anxiety and depression improve quality of life and support healthier behaviors.

BONE HEALTH
Estrogen maintains bone density and reduces osteoporosis risk.

Improvements are often interconnected and reinforce each other.

4. ESTROGEN'S BENEFICIAL PATHWAYS



5. EVIDENCE SUMMARY

OUTCOME AREA	EVIDENCE STRENGTH	COMMENTS
Mental Health & Quality of Life	★★★★★	Strong evidence of improvement in dysphoria, anxiety and depression.
Hematologic Changes	★★★★★	Well-established effect of estrogen.
Lipid Profile Improvement	★★★★☆	Consistent improvements reported in many studies.
Blood Pressure & Vascular Function	★★★★☆	Strong biological plausibility and supporting clinical data.
Glucose Metabolism	★★★☆☆	Improvement in some individuals; dependent on many factors.
Kidney Function (Lab Markers)	★★★☆☆	May improve or stabilize; creatinine lowering can reflect reduced muscle mass. Cystatin C recommended.
Diabetic Retinopathy	★☆☆☆☆	Limited direct evidence; improvements likely related to better glycemic and vascular control.

★★★★★ Strong ★★★★☆ Moderate ★★★☆☆ Limited ★★☆☆☆ Very Limited / Insufficient

6. CLINICAL CONSIDERATIONS

- Individualize hormone therapy.
- Monitor labs and clinical outcomes regularly.
- Control confounding factors (glucose, BP, lipids, weight, medications).
- Coordinate care with endocrinology, nephrology, ophthalmology and primary care.
- Consider both benefits and potential risks (e.g., thromboembolism, liver effects).

Kidney laboratory values

Estrogen has known biological effects that could indirectly influence kidney health in some situations, including effects on:

- Blood vessel function
- Inflammation
- Oxidative stress
- Renin-angiotensin-aldosterone system

Some experimental and observational studies suggest estrogen may have **protective vascular and renal effects**, but these findings are not sufficient to conclude that feminizing hormone therapy restores kidney function in transgender women. Kidney laboratory values (such as creatinine and estimated GFR) can also change after hormone therapy because muscle mass often decreases, reducing creatinine production. That can make kidney function appear improved even when the kidneys themselves have not changed. However an effect of reduced muscle mass, which lowers serum creatinine. In that case, creatinine-based estimates of kidney function can improve even if intrinsic kidney function has not changed. This therefore could cause ancillary lab values to decline to safer levels while maintaining the aforementioned intrinsic kidney function.

Another possibility is that estrogen indirectly improved vascular or inflammatory processes. There is experimental evidence that estrogen can influence:

- Endothelial function
- Nitric oxide production
- Oxidative stress
- Inflammatory signaling
- Renin-angiotensin system

These mechanisms are biologically plausible, but they have not been established as a treatment for chronic kidney disease in transgender women.

Diabetic retinopathy

This is where the evidence is much weaker as there is **no established clinical evidence** that estrogen therapy reverses diabetic retinopathy, but there appears plausible indirect benefits of estrogen therapy.

The strongest predictors of improvement or stabilization are:

- sustained glucose control,
- blood pressure control,
- lipid management,
- and appropriate ophthalmologic treatment when needed.

There is laboratory research suggesting estrogen has neuroprotective and vascular effects in the retina, but this has not been demonstrated as a treatment for diabetic retinopathy in clinical practice.

Although estrogen testing in **animal** studies and laboratory research suggest estrogen may have:

- neuroprotective effects,
- anti-inflammatory effects,
- antioxidant effects,
- retinal vascular effects.

Blood vessel function was noted in the kidney function analysis and would potentially link the the retinal vascular improvements.

General laboratory improvements

If multiple laboratory markers improved simultaneously to implementation of estrogen, then a broader physiological effect becomes more plausible.

Estrogen has known effects on:

- body composition,
- lipid metabolism,
- vascular function,
- insulin sensitivity (which can vary among individuals),
- inflammatory mediators,
- autonomic nervous system activity.

Those effects could influence laboratory values indirectly.

Could estrogen improve overall physiology?

This is where the overall hypothesis intersects with the neurodevelopmental discussion of this white paper.

One possible model is:

- If an individual's neuroendocrine system is more congruent with estrogen signaling because of prenatal development, then restoring an estrogen-dominant hormonal environment could improve:
    - psychological well-being,
    - stress physiology,
    - autonomic regulation,
    - sleep,
    - and indirectly influence metabolic health.

This is biologically plausible.

What has **not** been demonstrated is that estrogen directly reverses unrelated medical diseases because of prenatal neurodevelopment.

Mental health and stress

One area where evidence is considerably stronger is psychological well-being.

Many transgender women experience improvements in:

- gender dysphoria,
- depression,
- anxiety,
- sleep,
- and quality of life after appropriate hormone therapy.

Improved mental health can indirectly improve physical health by making it easier to maintain medication adherence, nutrition, exercise, sleep, and diabetes management.

What would strengthen the case?

From a research standpoint, the most convincing evidence would include:

- serial laboratory results before and after therapy,
- HbA1c measurements,
- blood pressure records,
- retinal imaging before and after treatment,
- kidney function measured using methods less affected by muscle mass (such as cystatin C-based estimates),
- medication history,
- and documentation showing no other significant changes.

Overall assessment

Characterization of the current evidence:

Outcome	Evidence that estrogen directly causes improvement
Reduction in gender dysphoria	**Strong**
Improved quality of life and mental health	**Strong**
Changes in routine laboratory values	**Strong** (expected physiological effects)
Direct improvement in kidney disease	**Limited**
Direct improvement in diabetic retinopathy	**Very limited**
Improvement in overall cardiometabolic health through indirect effects	**Moderate**, but depends heavily on individual factors

> *The close temporal relationship between initiation of estrogen therapy and improvements in multiple clinical measures, in the absence of major changes in diet, exercise, or environment, is consistent with estrogen being a contributing factor. While current biological knowledge provides several plausible mechanisms —such as effects on vascular function, inflammation, neuroendocrine regulation, and metabolism—the available evidence is insufficient to conclude that estrogen directly reversed kidney disease, diabetic retinopathy, or other systemic conditions. Further clinical investigation would be required to determine whether the observed improvements represent treatment effects, indirect physiological changes, or unrelated recovery.*

Subject matter experts (SME) referenced in this white paper

Subject Matter Expert	Qualifications	Institution / Affiliation (representative)	Primary Area of Expertise	Contribution Relevant to the Hypothesis
J. Graham Theisen	MD; Physician-Scientist	Augusta University (former affiliation)	Reproductive endocrinology, genetics	Candidate-gene studies; polygenic susceptibility models; hormone-signaling genetics
Vincent Harley	PhD; Molecular Geneticist	Hudson Institute of Medical Research	Molecular genetics; sex determination	Steroid hormone genetics; androgen receptor biology; developmental genetics
Julie Bakker	PhD; Professor of Neuroendocrinology	University of Liège	Developmental neuroendocrinology	Prenatal hormone effects on fetal brain sexual differentiation
Antonio Guillamon	MD, PhD; Professor Emeritus of Psychobiology	National University of Distance Education (UNED)	Neuroanatomy; psychobiology	Neurodevelopment; MRI and structural brain differences
Ivanka Savic	MD, PhD; Professor of Neurology	Karolinska Institute	Functional neuroimaging	Brain connectivity and structural imaging related to gender identity
Dick F. Swaab	MD, PhD; Neuroscientist	Netherlands Institute for Neuroscience	Neurobiology; hypothalamic development	Research on sexually dimorphic hypothalamic nuclei (including BSTc)
Alicia Garcia-Falgueras	PhD; Neuroscientist	Spanish neuroscience research institutions	Neurodevelopment	Sexual differentiation of the human brain; neuroanatomy
William Reiner	MD; Pediatric Urologist	University of Oklahoma (former)	Disorders of sex development	Clinical studies of prenatal hormone exposure and gender development
Peggy T. Cohen-Kettenis	PhD; Clinical Psychologist	Amsterdam UMC (former)	Developmental psychology	Longitudinal research on gender identity development
Joshua D. Safer	MD; Endocrinologist	Mount Sinai Health System	Endocrinology	Gender-affirming hormone therapy; endocrine physiology; clinical guidelines
Vin Tangpricha	MD, PhD; Endocrinologist	Emory University	Clinical endocrinology	Hormone therapy outcomes; metabolic effects of estrogen treatment
Guy G. T'Sjoen	MD, PhD; Endocrinologist	Ghent University Hospital	Endocrinology	Long-term outcomes of gender-affirming hormone therapy
Martin den Heijer	MD, PhD; Endocrinologist	Amsterdam UMC	Internal medicine; endocrinology	Longitudinal hormone therapy outcomes and safety
Richard Green	MD; Psychiatrist	Formerly UCLA and Charing Cross Hospital	Psychiatry	Early research on gender identity development
Norman Doidge	MD; Psychiatrist	University of Toronto	Neuroplasticity	Writings on brain plasticity; not

Subject Matter Expert	Qualifications	Institution / Affiliation (representative)	Primary Area of Expertise	Contribution Relevant to the Hypothesis
		(faculty affiliation)		a primary transgender genetics researcher but relevant to adaptive neural change

Organization within the white paper

Discipline	Representative SMEs
Developmental Biology & Neuroendocrinology	Julie Bakker, William Reiner
Molecular Genetics	J. Graham Theisen, Vincent Harley
Neuroanatomy & Brain Development	Antonio Guillamon, Dick F. Swaab, Alicia Garcia-Falgueras
Neuroimaging	Ivanka Savic
Clinical Endocrinology	Joshua D. Safer, Vin Tangpricha, Guy T'Sjoen, Martin den Heijer
Developmental Psychology & Psychiatry	Peggy T. Cohen-Kettenis, Richard Green

Subject matter experts (SME) notes

The experts listed above are recognized contributors to the fields of developmental biology, genetics, neuroendocrinology, neuroimaging, endocrinology, and gender medicine. Their published work contributes to individual components of the prenatal neurodevelopmental model discussed in this paper. Inclusion in this table should not be interpreted as indicating that each researcher endorses the complete integrated hypothesis presented here.

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