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Breastfeeding and Future Maternal Health-No Causal Evidence

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Letter to the Editor

In a recently published 30-year study, Gunderson et al. reported that increased lactation duration was significantly associated with reduced type 2 diabetes (T2D) incidence¹. The authors briefly mentioned but insufficiently discussed the potential role of prolonged hyperprolactinemia accompanying protracted breastfeeding in the reduced T2D incidence. Higher prolactin (PRL) levels in pregnancy independently predict a lower risk of postpartum prediabetes and T2D diabetes². PRL plays a role in beta-cell mass³, islet proliferation, insulin secretion and action, glucose regulation⁴, and feeding cycle; reduced PRL levels are associated with metabolic risk factors⁵ and impairments in men.

In a large population-based study, low PRL levels were significantly associated with T2D risk in men and women, and higher PRL levels with lower T2D risk⁶. The *PRL* gene 6p22.3 locus is associated with pre-diabetes traits and T2D. A variant near *PRL* is associated with male obesity and glycemic traits. The PRL-regulatory-element binding protein (*PREB*) gene is associated with eating disorders.

PRL action requires the PRL receptor (*PRLR*). *PRLR* knockout mice show reduced beta-cell mass during embryogenesis and postnatally. *PRLR* is key for glucose homeostasis, beta-cell mass maintenance, and islet adaptation in pregnancy. The *PRLR* gene 5p13.2 locus is linked to C reactive protein.

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Conflict of Interest

The authors have no conflict of interest to declare.

PRL secretion requires the PRL-releasing-hormone receptor (*PRLHR*), which is implicated in body weight; *PRLRH* knockout mice overeat, are insulin-resistant, and obese. In rats, a mutated *PRLRH* causes hyperphagia, obesity, and dyslipidemia. The *PRLRH* gene 10q26.13 locus is linked to T2D.

The PRL-pathway is also modulated by oxytocin (OXT) and the OXT receptor (OXTR), both of which may confer risk for PRL-pathway disruption and T2D.

OXT stimulates PRL via OXTR; hypothalamus OXTergic neurons are influenced by PRL via PRLR. *OXT* heterozygous knockout mice develop obesity and glucose intolerance. *OXT*, localized in rat pancreatic islets, has a role in alpha- and beta-cell secretion in diabetic and control subjects. Central OXT infusion in diet-induced obese rats causes weight loss, increases lipolysis, and reduces glucose intolerance. Exogenous OXT reduces obesity, reward-driven food intake in humans, and reverses pre-diabetes in mice and patients. The *OXT* gene 20p13 locus is linked to small LDL- and VLDL-particles in T2D and T2D.

OXTR-deficient mice develop obesity. The *OXTR* gene 3p25 is strongly associated with T2D, metabolic syndrome, and coronary-artery disease.

In summary, PRL and the PRL-pathway may be the key mediators for lactation-dependent T2D protection. *PRL*, *PRLR*, *PRLHR*, *OXT* and *OXTR* genes should be studied because they may confer T2D risk.

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