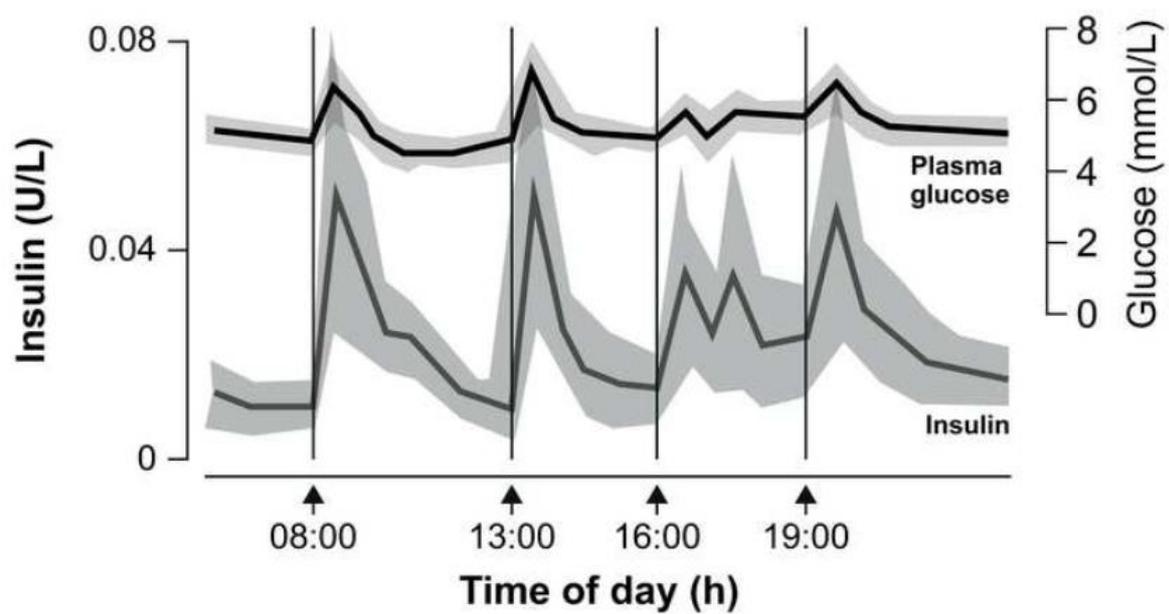


**Supplemental Material**

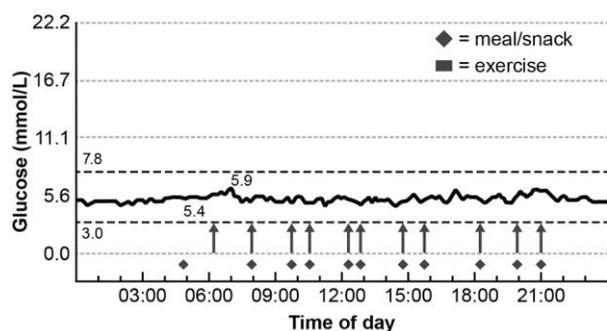
**Fig. S1** 24-hour plasma glucose and insulin profiles in healthy individuals (reprinted with permission from David Owens).



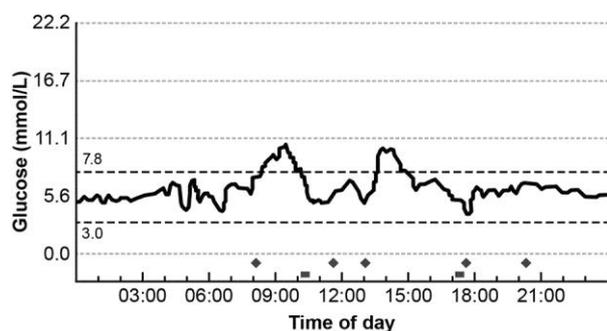
**Fig. S2** Progressive impairment of homeostatic mechanisms during development of T2DM. **a** Progression of impaired glucose tolerance (reprinted with permission from Markolf Hanefeld), and **b** Progression of impaired homeostatic mechanisms associated with impairment of glucose tolerance: i) plasma glucose, ii) plasma insulin, iii) C-peptide, iv) pro-insulin (reprinted with permission from Markolf Hanefeld).

**Fig. S2a**

**Normal glucose tolerance**



**Impaired glucose tolerance**



**Advanced T2DM**

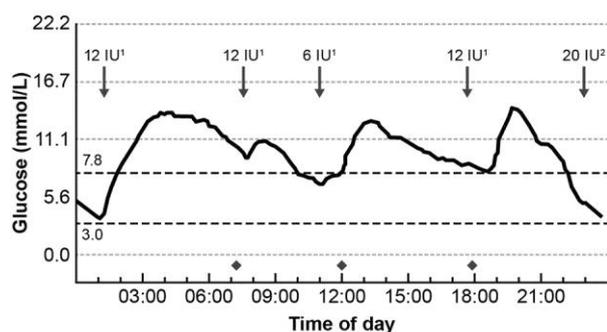
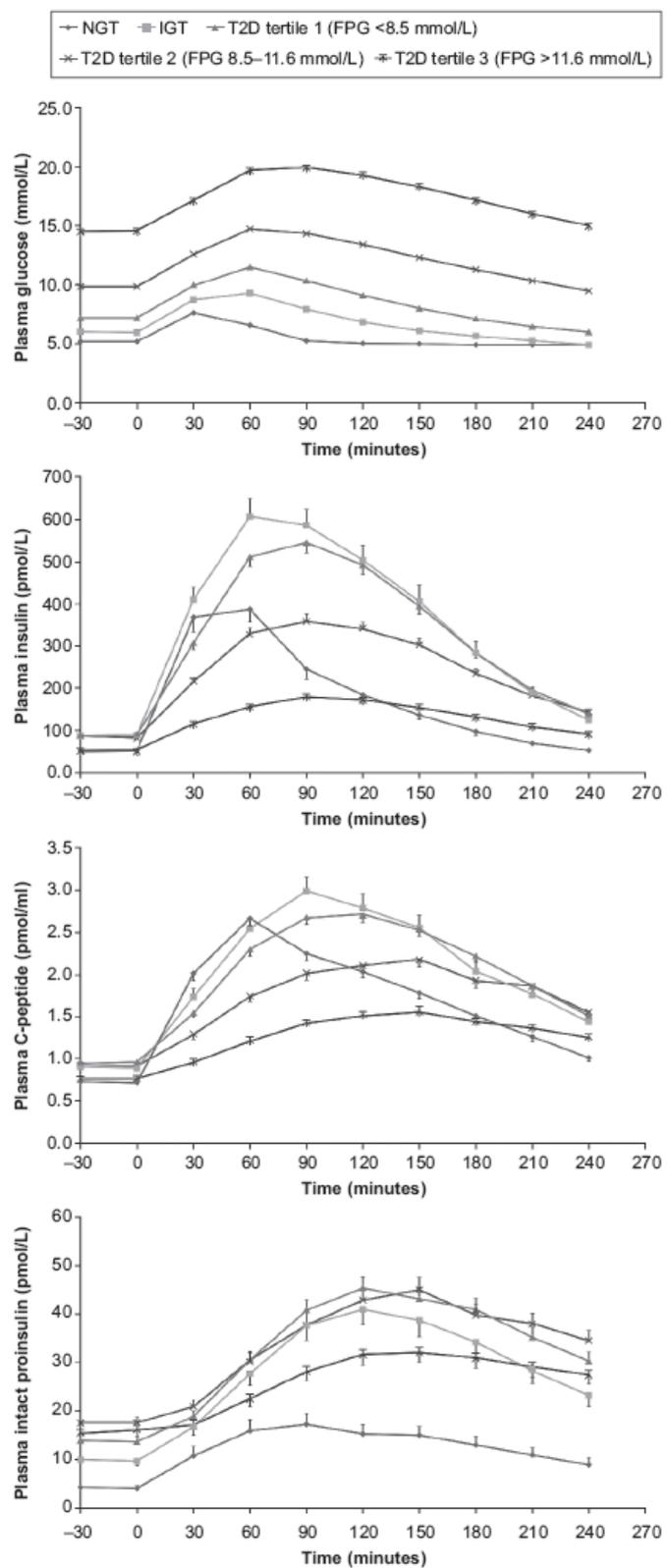


Fig. S2b



**Table S1** Studies of the effects of early insulin treatment on  $\beta$ -cell function in patients newly or recently diagnosed with T2DM

Publication	Study type	Treatment duration	Patient population	Treatment	Outcome
Li Y et al. 2004 [46] Xu et al. 2009 (2-year follow-up) [52]	Open-label	2 weeks	Severely hyperglycemic (n = 138)	Short-term intensive insulin	Preservation of $\beta$ -cell function at 2 years (HOMA-B)
Weng et al. 2008 [42]	RCT	2 weeks	Severely hyperglycemic (n = 382)	Short-term intensive insulin vs. OAD	Significant increase in $\beta$ -cell function in both groups (HOMA-B)
Lingvay et al. 2009 [47] Harrison et al. 2012 (3.5-year follow-up) [45]	Open-label intensive, then RCT vs. OAD	3 months	Relatively well controlled (n = 58)	Intensive insulin + OAD	Preservation of $\beta$ -cell function at 3.5 years (C-peptide and glucose)
Chon et al. 2010 [53]	Retrospective cohort	5 months (mean)	Severely hyperglycemic (n = 61)	Intensive and non-intensive insulin	Significant increase in $\beta$ -cell function (HOMA-B)
Mu et al. 2012 [48]	RCT	3 months	Severely hyperglycemic (n = 129)	Non-intensive insulin + OAD vs. OAD	Significant increase in $\beta$ -cell function vs. OAD (HOMA-B)
Pistrosch et al. 2013 [50]	Open-label	36 weeks	Mildly hyperglycemic (n = 75)	Long-term non-intensive insulin vs. OAD	Significant increase in $\beta$ -cell function vs. OAD (HOMA-B)
Kramer et al. 2013 [41]	Open-label	4 weeks	Relatively well controlled (n = 63)	Short-term intensive insulin	Significant increase in $\beta$ -cell function (ISSI-2)

*HOMA-B* Homeostasis Model Assessment-B, *ISSI-2* insulin secretion sensitivity index, *OAD* oral antidiabetes drug, *RCT* randomized controlled trial, *T2DM* type 2 diabetes mellitus