

Appendix 4: Prevention and treatment of less common adverse effects reported with insulin			
Adverse effect	Description	Evidence level	Prevention and treatment
Congestive heart failure (CHF) ¹	<ul style="list-style-type: none"> CHF rates were highest in regimens that included insulin and lowest in regimens including metformin Addition of insulin to preexisting diabetes regimens significantly increased the rates of CHF relative to the addition of sulfonylureas (odds ratio [OR] 2.33, $p < 0.0001$) and metformin (OR 2.66, $p < 0.0001$) even after adjustment for relevant covariates 	27-mo observational study	Conventional medical management for CHF as needed
Edema ^{2,3}	<ul style="list-style-type: none"> Varies from mild peripheral edema to frank anasarca 	Case reports	Self-limiting, rarely requires treatment except for diuretic use with anasarca
Lipodystrophy ^{4,5}	<ul style="list-style-type: none"> Most common cutaneous effect of insulin Consists of subcutaneous fat at injection sites Occurs in 3.6% of patients with type 2 diabetes and 28.7% of patients with type 1 diabetes Risk factors include: young age, low body mass index, abdominal injection site, and failure to rotate injection sites 	Case reports	<p>Prevention:</p> <ul style="list-style-type: none"> Regular rotation of injection sites. <p>Treatment:</p> <ul style="list-style-type: none"> Rotation of injection sites and switching to rapid-acting insulin analogues so potential regression of affected sites may occur Insulin pump therapy Syringe assisted liposuction
Other cutaneous reactions ⁶	<p>Lipoatrophy:</p> <ul style="list-style-type: none"> Associated with older less purified insulin Rare with modern insulins Risk factors include: young age, individuals with previous dermal reactions to insulin <p>Skin abscesses, pigmentation, and keloid formation:</p> <ul style="list-style-type: none"> Rare 	Case reports	<p>Lipoatrophy:</p> <ul style="list-style-type: none"> Prevention: regular rotation of injection sites Treatment: injection of a modern insulin into the edge of the area, co-administration of insulin with dexamethasone (4 mcg/unit) or switching to insulin pump therapy <p>Skin abscesses:</p> <ul style="list-style-type: none"> Prevention: good hygiene and appropriate antiseptic measures, rotation of injection site
Allergic reactions and formation of antibodies to insulin ⁷⁻¹²	<ul style="list-style-type: none"> Associated with older less purified insulin Rare with modern insulins 	Case reports	<p>Cutaneous allergic reactions:</p> <ul style="list-style-type: none"> Tend to be short-lived and resolve spontaneously within a few weeks Antihistamines or corticosteroids if needed Switching insulin used (avoid use of insulins containing zinc or protamine) Dividing of dose and varying delivery sites Addition of 1 mcg dexamethasone to each unit of insulin per injection Use of insulin pump therapy Insulin withdrawal Densitization in more serious cases
Other adverse effects	<ul style="list-style-type: none"> Insulin-induced transaminitis¹³ (> 10 times the upper limit of normal) Reversible nephrotic syndrome¹⁴ Beta-cell destruction¹⁵ (complete disappearance of C-peptide upon insulin initiation) 	Case reports	No specific prevention nor treatment strategy to avoid

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