

Review Article:

Androgen Deprivation Therapy Increases the Risk of Diabetes and Non- cancer Mortality in Prostate Cancer patients: A Meta-analysis

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Abstract:

Androgen deprivation therapy (ADT) with Luteinizing hormone releasing hormone analogues or bilateral subcapsular orchiectomy is the mainstay of treatment in high risk localized and metastatic prostate cancer along with other modalities. ADT is associated with increased fat mass and insulin resistance, but the risk of incident diabetes and non-cancer mortality during this treatment has not been well studied. We conducted a meta-analysis to see whether androgen deprivation therapy is associated with an increased incidence of diabetes and cardiovascular diseases. The MEDLINE, CANCELIT, COCHRANE library database, and the search engines, were searched to identify, prospective, randomized, controlled studies in prostate cancer patients receiving short, long term or no ADT and risk of incident diabetes and non cancer mortality. Comprehensive Meta-analysis software version 2.0 was used for the analysis. Four prospective trials with a total patient population of 1, 15,119 were identified. Pooled results from these trials showed an increased risk of diabetes in patients treated with long term ADT ($p = 0.0001$) as well as increased non-cancer mortality (Odds ratio 1.69; $p < 0.001$). Main cause of non-cancer death was sudden cardiac death (SCD). The resultant funnel plot of meta-analysis showed lack of publication bias. This meta-analysis shows increased risk of diabetes and cardiovascular diseases in prostate cancer patient on long term androgen deprivation therapy; already existing diabetes also deteriorated. The results of this study warrants active surveillance of patients on androgen deprivation therapy.

Key words: Androgen deprivation therapy, Prostate cancer, Risk of diabetes, Cardiovascular diseases, Meta-analysis

Introduction:

Prostate cancer is one of the most common cancers in men worldwide [1]. However, due to unavailability of national based cancer registries, its exact incidence or prevalence is not known in our country. We reported that majority of patients in Pakistan present with advanced and metastatic stage (70%); only 30% of cases were localized or locally advanced [2]. Androgen deprivation therapy (ADT) is used along with radiotherapy and surgery in localized or locally advanced cases and as a monotherapy in metastatic cancer [3].

Although its use has resulted in improved survival in some patients, ADT has negative consequences [4]. Recent studies have also found metabolic complications in these men [5].

Studies show that short-term ADT (3–6 months) results in development of hyperinsulinemia without causing hyperglycemia and long term (≥ 12 months) ADT reveal higher risk of incident diabetes and metabolic syndrome compared with controls [6,7]. In addition, men undergoing ADT also experience higher cardiovascular mortality. Few prospective studies with reasonable longer follow up of ADT have documented the timing of onset of these complications and strategies to prevent those complications [8]. Some centers have adopted a practice of doing the baseline and serial screening for fasting glucose and other cardiac risk factors in prostate cancer patients receiving ADT and in selected cases, glucose tolerance testing and cardiac evaluation [9].

The possible mechanism for increased risk of diabetes and cardiovascular diseases in patients

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on ADT is that ADT results in a decline in lean body mass and an increase in fat mass, subsequently this adiposity via elaboration of adipokines and inflammatory cytokines results in hyperinsulinemia and hyperglycemia [10]. A recent population-based study found that men undergoing ADT with luteinizing hormone releasing hormone (LHRH) analogues had a higher risk of incident diabetes, coronary artery disease, myocardial infarction, and sudden death. In contrast surgical castration (orchiectomy) was associated only with a higher risk of diabetes [11]. The increased risk of cardiovascular events with LHRH analogues could be partly because of pure drug effect, because these have been shown to possess arrhythmogenic potential [12]. Another retrospective study using a claims-based database showed that prostate cancer patients on ADT were 36% more likely to develop incident diabetes compared to non-ADT patients [13]. Interestingly majority of these incident diabetes and cardiovascular events were self reported. Also most studies were small. We therefore conducted a meta-analysis that assessed whether long term ADT led to higher risk of diabetes and cardiovascular diseases in locally advanced and metastatic prostate cancer patients. We also attempted to review non-cancer mortality risk in prostate cancer patients on ADT.

Materials and methods:

Studies and study population:

The search criteria for studies had to be either complete articles of prospective, randomized, controlled trials or retrospective if these were well controlled. The abstracts from which full details were available were also included. The MEDLINE, CANCELIT, and Cochrane library databases were searched (period 1990- 2009) using the terms "(diabetes or diabetic), (prostate cancer, carcinoma), (Hormonal therapy, medical castration, surgical castration, Luteinizing/gonadotropin hormone releasing hormone agonist/analogues, orchiectomy) and the risk". These terms were then combined for search for prospective, retrospective, randomized, controlled, review and meta-analysis. The relevant articles were selected by two methodologists. Only studies which met the following criteria were included.

The patients had to have histologically confirmed adenocarcinoma prostate cancer and have

received androgen deprivation therapy either, medical or surgical after the radical prostatectomy or radiotherapy and as monotherapy in metastatic disease.

Outcome measures:

The outcome measures were risk of incident diabetes, risk of cardiovascular diseases and non prostate cancer mortality.

Review analysis:

All analyses were carried out on an intention to treat analysis basis. For the categorical variables, weighted risk ratios and their 95% confidence intervals (95%CI) were calculated using comprehensive meta-analysis software. The results were tested for heterogeneity at the significance level of $p < 0.05$. If there was evidence of heterogeneity, a random effects model was used for meta-analysis; otherwise fixed effects model was used. The odds ratio and 99% CI were calculated for each trial and presented in forest plot.

We determined the risk of incident diabetes and cardiovascular diseases based on the follow up period mentioned in each trial. We also determined the percentage of non cancer related deaths.

Publication bias was evaluated using the funnel graph, the Begg-Mazumdar adjusted rank correlation test [14], and the Egger test [15]. For heterogeneity we performed the Cochran's Q test to determine whether the studies are homogenous. All analyses were performed using comprehensive meta-analysis software.

Results:

The electronic search revealed 344203 relevant citations, among which 752 diabetes and androgen deprivation therapy related studies were selected. After screening, 21 full text articles were retrieved for further assessment. Finally, four studies were identified that met criteria (diagram 1); total population of these studies was 1, 15,119 patients. Details are given in Table 1.

The cumulative risk of Diabetes and cardiovascular diseases:

All four studies with population of 1, 15,119 patients, analyzed the cumulative risk of diabetes and cardiovascular diseases as one of the outcomes. The risk was significantly high in patients receiving long term ADT ($p = 0.0001$). The pooled odds ratio was 1.64 (95%CI 1.54- 1.74).

Diagram 1. Schema of meta-analysis

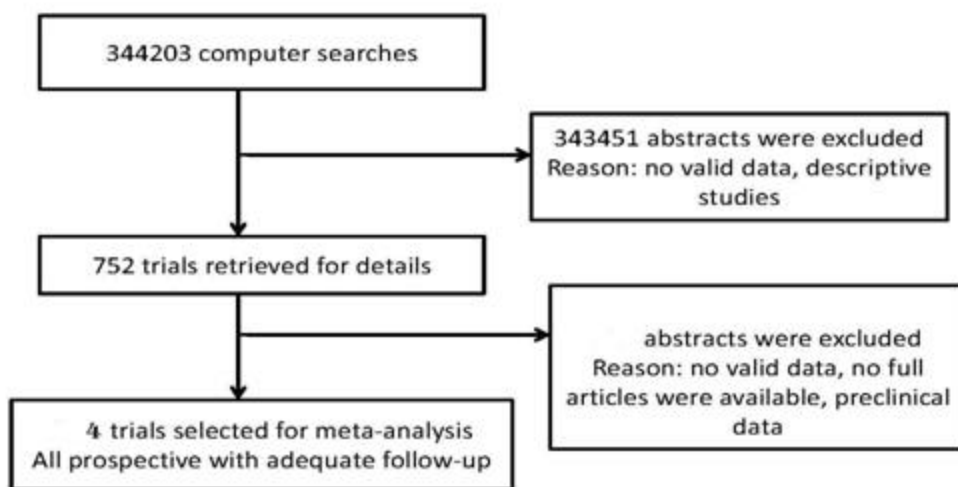


Table 1. Prospective trials in prostate cancer with androgen deprivation (ADT) therapy included in the meta-analysis

Study Sample size (N)	Year	Median age	Hormonal therapy	Follow up (median)
RTOG 92-02 ¹⁴ N=1,554	1992-2000	70.0 years	LHRH analogues	8.1 years
Massachusetts study ¹⁵ N= 73,196	1992-1999	74.2 years	LHRH analogues/BSO	4.55 years
Toronto study ¹⁶ N= 38,158	1995-2005	75.0 years	LHRH analogues/BSO	6.47 years
Rotterdam trial ¹⁷ N=2,211	1993-1999	65.97 years	LHRH analogues/BSO	5.5 years

Figure 1. Meta-analysis of four prospective trials in prostate cancer showing increased risk of incident diabetes, cardiovascular diseases with long term androgen deprivation therapy.

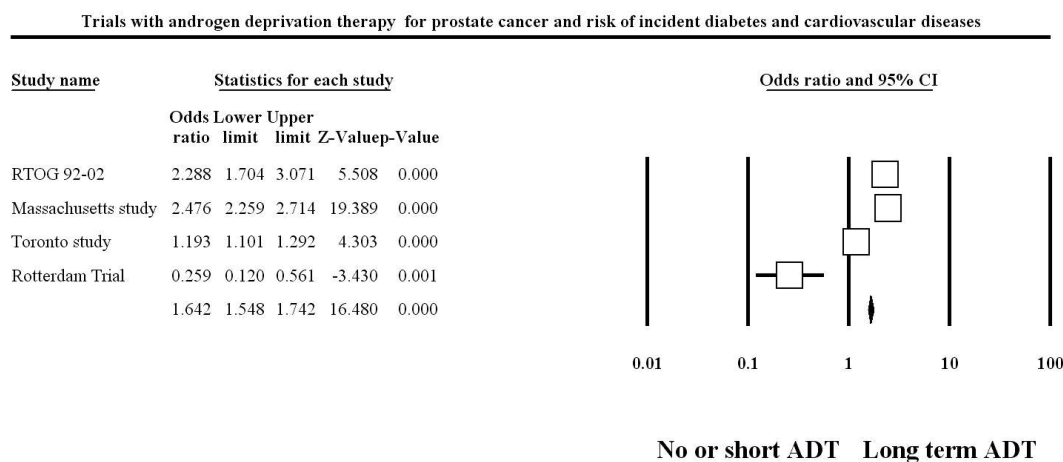


Figure 2. Meta-analysis of four prospective trials in prostate cancer showing increased risk of non prostate cancer mortality with long term androgen deprivation therapy

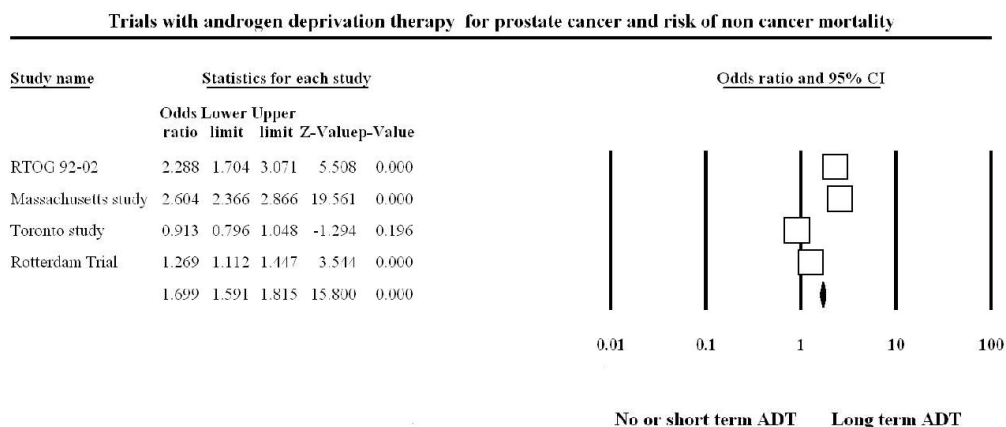
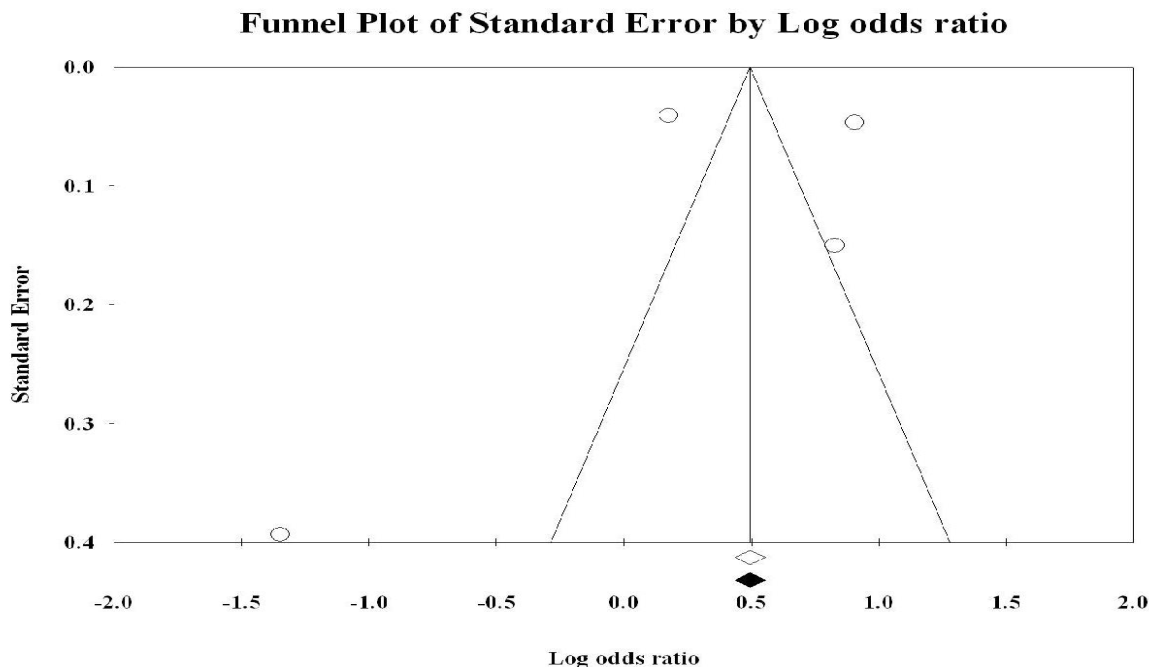


Figure 3. Funnel plot of publication bias



The result of the test for heterogeneity was not statistically significant ($p=0.14$) as shown in Fig. 1. Further subgroup analysis showed odds ratio (OR 1.16 95%CI 1.11-1.21, p 0.001) for diabetes and odds ratio of 2.12(95% CI 1.69-2.66 p <0.0001) for cardiovascular diseases in patients receiving androgen deprivation therapy.

Non-prostate cancer mortality:

All the included studies with patients number of 1, 15,119, examined the non prostate cancer mortality as one of the outcomes. The non cancer

mortality was significantly high in patients receiving long term androgen deprivation therapy, with a pooled odds ratio of 1.69 (95%CI 1.59-1.81, p value <0.0001). There was no significant heterogeneity (Fig. 2).

Publication bias:

The funnel plot found expected funnel shaped (Fig.3), showing three large studies on top of funnel with no significant publication bias (p values from Begg-Mazumdar test and Egger test were 0.27 and 0.14 respectively).

Discussion:

The increased risk of incident diabetes and cardiovascular diseases and related mortality after ADT has remained controversial; there are no guidelines to prevent these complications. This was the reason to take up this meta-analysis, with the basic purpose of obtaining a large enough sample size from different studies, to reveal a possible significant difference between long term androgen deprivation therapy (medical or surgical) and no or short term androgen deprivation therapy in terms of incident diabetes, cardiovascular diseases and non prostate cancer mortality in prostate cancer patients. In this meta-analysis, we selected all well controlled prospective studies with enough sample size and reasonable follow up published till date. The pooled analysis showed increased risk of diabetes and cardiovascular diseases and associated mortality.

In this meta- analysis, study by Keating et al from Massachusetts General hospital showed significant odds ratio 2.47 (95% CI 2.25-2.71) for androgen deprivation related diabetes and cardiovascular diseases [15]. In contrast the Rotterdam randomized trial showed no increased risk of diabetes, cardiovascular diseases or of dying of these diseases (odds ratio 0.25, 95%CI 0.12-0.56) [17]. But the latter trial was criticized due to selection bias, as the recruitment was based on volunteers.

The results of this meta-analysis as well as other trials which were not included in this study (table.2), are of considerable concern to patients and oncologists as these co-morbidities exacerbated by ADT become a greater threat to survival than the prostate cancer itself .Different studies have suggested that the periodic diabetic screening and regular exercises could be an effective method to prevent these complications [22,23].

Table.2: effects of androgen deprivation therapy on insulin, blood glucose levels and lipid profile in various studies

Study	Number of patients	Duration of ADT	Insulin Levels	Hyperglycemia	Lipid profile	comments
Smith JC, et.al [18] Cardiff, UK 2001	22	3months	63% rise after ADT <i>p 0.02</i>	None	No change	Fat mass rise seen after ADT
Dockery F, et.al [19] Hammersmith Hospital, UK 2003	16	3 months	63% rise after ADT <i>P 0.005</i>	None	Rise in triglycerides and cholesterol	Arterial stiffness was seen
Basaria S, et.al [20] Maryland, USA 2006	53	12- 24 months	Rise in insulin <i>P <0.001</i>	High <i>P 0.002</i>	Not measured	Rise in body mass index Rise in leptin levels in ADT patients
Smith MR, et.al [21] Boston, USA 2006	25	3 months	Rise in insulin <i>P 0.04</i> Decrease in insulin sensitivity index <i>P 0.02</i>	None	Rise in triglycerises, Total cholesterol	Glycosylated Hb rise <i>P < 0.001</i>

One criticism of our meta-analysis can be the possibility of type 1 (a error) or false positive results; care was taken to reduce this error by using Hunter-schmidt's approach, in which the effect size error is divided by the square root of the reliability coefficient of the dependent variables.

Looking at literature, androgen suppression therapy (ADT), is beneficial in prostate cancer; the range of its metabolic complications is increasing, especially incident diabetes, cardiovascular morbidity and associated mortality, which warrants the active involvement of diabetologists in cancer care.

Conclusion:

In view of this meta-analysis and magnitude of the problem of prostate cancer and relatively frequent use of androgen deprivation therapy, it is important for oncologists to be aware of common side effects, prevention, and treatment to improve quality of life and reduce morbidity and mortality in patients with prostate cancer and need for frequent diabetic and cardiac screening as a part of multi-modality discipline.

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